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16. ABSTRACT
Studies designed to test the ability of environmental pollutants to induce lung cancer in experimental animals by chronic inhalation exposure are summarized in this review. The studies are limited to those published in peer-reviewed journals and may not include all experiments conducted by chemical or pharmaceutical manufacturers to test product safety. These studies are also limited to those using small laboratory animals, e.g., Syrian Golden hamsters, mice and rats. The advantages and disadvantages of these species for use in respiratory carcinogenesis studies are discussed. Chemical substances reviewed include organic compounds, inorganic metallic and nonmetallic compounds, and complex mixtures. The results of these studies have shown that cancer of the respiratory tract can be induced by a wide variety of chemicals, many of which are present in ambient air. With few exceptions, substances that have been shown to induce lung cancer in humans have also proven to be carcinogenic in laboratory animals. Known animal carcinogens, however, have not always been shown to induce lung cancer in humans, because of inadequate testing and exposure and a lack of epidemiology data on lower sensitivity in humans. Inhalation carcinogenicity testing is both expensive and time-consuming limiting the number of chemicals that can be tested adequately. The development of shorter-term, lower-cost tests will allow an accurate appraisal of the carcinogenic potency of the numerous chemicals being produced and released into the environment.

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Experimental Respiratory Carcinogenesis in Small Laboratory Animals

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CONTENTS. I. Introduction. II. Relative advantages and disadvantages of mice, rats and Syrian hamsters for use in respiratory carcinogenesis. III. Organic chemicals. IV. Inorganic metallic compounds. V. Inorganic nonmetallic compounds. VI. Complex mixtures. VII. Summary and conclusions. VIII. References.

I. INTRODUCTION

One of the major efforts in toxicological research has been an assessment of the importance of various environmental factors in the induction of cancer. Much of the present interest in this topic has been due to the rapidly increasing numbers of chemicals being synthesized and produced in manufacturing processes, as well as increasing pollution from combustion sources. Since many of the pollutants are airborne, studies assessing their effects via the inhalation route have assumed a major importance.

Respiratory carcinogenesis was the primary topic at an International Conference on Lung Tumors in Animals, held at Perugia, Italy, in 1965, and at the U.S. Atomic Energy Commission Conference on Inhalation Carcinogenesis, Gatlinburg, Tennessee, in 1969. Sunderman (1971, 1977, 1978) included inhalation studies in his reviews of metal carcinogenesis. Homburger (1979) reviewed chemical carcinogenesis, including respiratory carcinogenesis in the Syrian hamster. No recent conferences or reviews, however, specifically concerning cancer induction via the inhalation route have been conducted.

This review addresses, primarily, the effects of inhaled chemicals, with the exception of radioactive compounds, upon induction of respiratory tract cancer in small laboratory animals. With certain chemicals such as vinyl chloride, where lung tumors are not always the major endpoint, a discussion of tumors at other locations is also included. Studies not included are those in which respiratory tract tumors have been induced by means other than inhalation, inhalation toxicology studies designed to address nononcogenic endpoints, or studies of such short duration that the development of lung tumors would be considered very unlikely.

The decision to include a study based upon duration was, of necessity, somewhat arbitrary. Strain A mice, for example, are seldom exposed for more than 6 months because of rapidly increasing tumor rates among control animals. The highly lung tumor-resistant C57BL strain, on the other hand, often requires a

lifetime exposure to achieve positive results. This review is limited to small laboratory animals, primarily mice, rats, and Syrian golden hamsters.

It was difficult to categorize the studies into classes based strictly on the composition of the substances being tested. Certain experiments such as those using pure organic chemicals could readily be classified into one group. Many of the experiments, however, involved exposure to complex mixtures. These often included both inorganic and organic compounds as liquid or solid aerosols. Most of the complex mixtures were the result of various combustion processes. Thus, certain types of chemicals such as the polycyclic aromatic hydrocarbons are likely to be found in many of these mixtures. Classification of complex mixtures into cigarette smoke, ambient air, engine emissions, and other fossil-fuel-derived products was admittedly somewhat arbitrary and was based on the source of pollutant, recognizing that their chemical composition was not mutually exclusive.

II. RELATIVE ADVANTAGES AND DISADVANTAGES OF MICE, RATS OR SYRIAN HAMSTERS FOR USE IN RESPIRATORY CARCINOGENESIS STUDIES

Until recently the mouse had been the most commonly used model for respiratory tract carcinogenesis studies. Its advantages included small size, allowing use of larger exposure groups, and a somewhat shorter lifespan than rats or hamsters. Many strains with widely varying sensitivity to lung tumor induction are also available (Bickerton, 1974). Finally, some strains, such as the A, are not only extremely sensitive to tumor induction but also develop tumors in a relatively short time (Shimkin and Stoner, 1975). The use of the mouse has been criticized because the primary tumor type found in sensitive strains, the pulmonary adenoma, is relatively rare in humans. Since these tumors develop spontaneously, there is also concern as to whether an increase in tumor incidence is due to initiation or to promotion of an already initiated process.

Syrian hamsters have the advantage of being quite resistant to pulmonary infection, have a very low spontaneous lung tumor incidence, and develop tumor types very similar to those of humans (Saffiotti *et al.*, 1968; Dontenwill *et al.*, 1973; Pour *et al.*, 1976). Although the hamster is an ideal model in many respects, it is relatively insensitive to the induction of lung cancer. As a result, most studies using this species, especially those involving exposure to cigarette smoke, have not produced definitive results. The development of a hamster strain sensitive to the induction of laryngeal cancer may help to alleviate this deficiency (Bernfeld *et al.*, 1974, 1979). The increased sensitivity of this strain, however, needs to be confirmed by others.

The rat has been favored in more recent studies. This is partially due to the sensitivity of this species to induction of nasal cancer by organic chemicals, a subject of great interest at present. Rats also have a low incidence of spontaneous respiratory tract tumor development. Finally, the neoplastic alterations are considered to be sufficiently similar to those found in humans to render it a good model for human lung cancer (Laskin *et al.*, 1975).

III. ORGANIC CHEMICALS

Results of studies discussed in this section are summarized in Table 1.

Acetaldehyde. Feron (1979) exposed male Syrian Golden hamsters, 210/group, 7 hr/day, 7 days/week for 52 weeks to either clean air or 1500 ppm acetaldehyde. They were then held an additional 26 weeks in clean air. The controls and experimentals were further divided into 6 groups of 35 animals each and given weekly intratracheal instillations of 0.0625, 0.125, 0.25, 0.10, or 1.0 mg benz(*a*)pyrene (BaP) during the 52 weeks of exposure to acetaldehyde. The tumor incidence was zero in hamsters exposed to acetaldehyde alone. Benz(*a*)pyrene induced a dose-dependent increase in lung tumor incidence which was not potentiated by inhalation of acetaldehyde.

Feron *et al.* (1982) conducted a second experiment in which Syrian Golden hamsters, 30/sex/group, were exposed 7 hr/day, 5 days/week for 52 weeks to acetaldehyde and then held an additional 29 weeks. The initial concentration of 2500 ppm was gradually reduced to 1650 ppm by the final 7 weeks of exposure. Individual groups received either no further treatment, intratracheal instillation of 18.2 or 36 mg BaP divided into 52 weekly doses (0.35 or 0.70 mg/dose), or subcutaneous injection of 2.1 μl diethylnitrosamine (DENA) divided into 17 doses (0.12 μl/dose). Among animals receiving acetaldehyde alone, 8 respiratory tract, 2 laryngeal, and 2 nasal tumors were detected in males compared with none among controls ($P < 0.05$). Acetaldehyde also markedly enhanced the incidence of BaP-initiated tracheobronchial carcinomas but did not influence the development of DENA-initiated tumors of the respiratory tract.

Acrolein. Feron and Kruysse (1977) studied the carcinogenic effects of acrolein vapor using a similar design as the acetaldehyde studies. Six-week-old Syrian Golden hamsters were exposed 7 hr/day, 5 days/week for 52 weeks to either clean air or 4 ppm acrolein and then held for an additional 29 weeks. The 252 animals in each group, half male and half female, were further divided into 4 groups of 63 animals each and given weekly intratracheal instillations of either 0.35 or 0.70 mg BaP for 52 weeks, subcutaneous injections of 0.135 mg diethylnitrosamine (DENA) every 3 weeks, or no further treatment. No lung tumors were detected among animals exposed to clean air or acrolein alone. Both BaP and DENA treatment resulted in a high incidence of lung tumors. The effects, however, were not potentiated by acrolein inspiration.

Acrylonitrile. Maltoni *et al.* (1977a) exposed Sprague–Dawley rats, 30 of each sex/group, to 5, 10, 20, or 40 ppm acrylonitrile (vinyl cyanide) 4 hours/day, 5 days/week for 12 months. Following completion of exposure they were held for a lifetime. A slight increase in the incidence of mammary tumors, foreskin papillomas, and skin carcinomas was noted in the exposed groups. No lung tumors were reported. According to the authors, the evidence for enhancement of tumorigenesis was inconclusive.

Benzo(a)pyrene. BaP was one of the earliest known carcinogens and one of the most extensively studied. While a variety of experiments have been conducted using intratracheal instillation of BaP, such as the acrolein and acetaldehyde studies, few have included the inhalation route. Laskin *et al.* (1970) exposed 20

TABLE 1

ONCOGENIC RESPONSE FROM INHALATION OF ORGANIC CHEMICALS

Compound	Species and strain	Exposure levels	Duration of exposure	Response	Primary tumor type(s)	References
Acetaldehyde	Hamsters, Syrian Golden	1500 ppm	12 mo	Negative	—	Feron, 1979.
Acetaldehyde	Hamsters, Syrian Golden	1650–2500 ppm	12 mo	Positive	Laryngeal carcinoma	Feron *et al.*, 1982.
Acrolein	Hamsters, Syrian Golden	4 ppm	12 mo	Negative	—	Feron and Kruysse, 1977.
Acrylonitrile	Rats, Sprague–Dawley	5–40 ppm	12 mo	Slight enhancement of some tumor types	Mammary tumors; forestomach papillomas; skin carcinomas	Maltoni, 1977.
BaP + SO_2	Hamsters, Syrian Golden rats, Sprague–Dawley	6 ppm SO_2 + 18 mg/m^3 BaP	Lifetime	Positive for rats only	Lung squamous cell carcinoma	Laskin *et al.*, 1970, 1976.
BaP	Hamsters, Syrian Golden rats, Sprague–Dawley	2–50 mg/m^3	14 mo	Negative	—	Mohr, 1978.
BaP + NaCl	Hamsters, Syrian Golden rats, Sprague–Dawley	2.2–46.5 mg/m^3	Lifetime	Highly positive	Squamous cell carcinoma upper respiratory tract	Thyssen *et al.*, 1981.
Benzene	Mice AKR/J and C57B1/6J	100 and 300 ppm	Lifetime	Negative	—	Snyder *et al.*, 1980.
BCME	Hamsters, Syrian Golden	1 ppm	6 hr, 6 wk	Marginal increase	Nasal esthesioneuroepithelioma	Drew *et al.*, 1975, Laskin *et al.*, 1971.
BCME	Hamsters, Syrian Golden	0.1 ppm	16 wk	Negative	—	Kuschner *et al.*, 1975.
BCME	Mice, A/H	1 ppm	21 wk	Positive	Pulmonary adenomas	Leong *et al.*, 1971.
BCME	Rats, Sprague–Dawley mice, ICR	0.001, 0.01, 0.1 ppm	6 mo	Significant increase at highest dose level	Pulmonary adenoma and adenocarcinoma in mice; nasal esthesioneuroepithelioma in rats	Leong *et al.*, 1971.
BCME	Rats, Sprague–Dawley	0.1 ppm	2–20 wk	Positive	Lung squamous cell carcinoma; nasal esthesioneuroepithelioma	Kushner *et al.*, 1975.
BCME	Rats, Sprague–Dawley	0.1 ppm	6 wk	Positive	Lung squamous cell carcinoma; nasal esthesioneuroepithelioma	Dulak and Snyder, 1980.
CCME	Hamsters, Syrian Golden	1 ppm	Lifetime	Negative	—	Laskin *et al.*, 1975.
CMME	Rats, Sprague–Dawley	1 ppm	6 wk	Marginal increase	Lung squamous cell	Drew *et al.*, 1975.
CMME	Mice, A/H	2 ppm	6.5 mo	Marginal increase	Pulmonary adenomas	Leong *et al.*, 1971.
Diazomethane	Rats, Porton, LAK mice, A/26	Unspecified	Up to 6 mo	Positive	Pulmonary adenomas	Schoental and Magee, 1962.
DBCP	Rats, Fischer 344 mice, B6C3	0.6 and 3.0 ppm	24 mo	Positive good dose response	Nasal cavity adenomas; squamous cell carcinomas; adenocarcinomas	Reznik *et al.*, 1980a.
DCE	Rats, Sprague–Dawley mice, CDI	6 ppm	12 mo	Negative	—	Lee *et al.*, 1977.

TABLE 1—*Continued*

Compound	Species and strain	Exposure levels	Duration of exposure	Response	Primary tumor types(s)	References
DCE	Rats, Sprague–Dawley mice, Swiss	24 ppm, mice 25–200 ppm, rats	12 mo	Positive in rats only	Kidney adenosarcoma; no lung tumors	Maltoni, 1977.
DCE	Rats, Sprague–Dawley mice, Swiss	10–150 ppm, rats 10–25 ppm, mice	12 mo	Positive in rats positive at 25 ppm in mice	Mammary tumors	Maltoni *et al.*, 1977b.
DCE	Rats, Sprague–Dawley mice, CDI	55 ppm	10 mo	Negative	—	Hong *et al.*, 1981.
DMCC	Hamsters, Syrian Golden	1 ppm	Lifetime	Highly positive	Nasal squamous cell carcinoma	Sellakumar *et al.*, 1980b.
DMCC	Rats, Sprague–Dawley	1 ppm	6 wk	Positive	Unspecified	Dulak and Snyder, 1980.
DMS	Rats, Sprague–Dawley mice, NMR hamsters, Syrian Golden	0.5 ppm	15 mo	Positive response but tumor incidence in each species uncertain	Nasal carcinoma; lung carcinoma	Schlögel and Bannasch, 1970.
EDB	Rats, mice	10 and 40 ppm	18–24 mo	Positive in rats only	Nasal carcinoma	NCI, 1981.
Epichlorhydrin	Rats, Sprague–Dawley	30 ppm, lifetime 100 ppm, 6 wk	Lifetime 6 wk	100 ppm, positive; 30 ppm, marginal increase	Nasal squamous cell carcinoma	Laskin *et al.*, 1980.
Ethylene oxide	Rats, Fischer 344	10, 22, 100 ppm	24 mo	Positive	Peritoneal mesothelioma; leukemia	Snellings *et al.*, unpublished report.
Formaldehyde	Mice, C3H	27–83 ppm	8 and 16 mo	Negative	—	Horton *et al.*, 1963.
Formaldehyde	Rats, Sprague–Dawley	14.7 ppm formaldehyde + 10.7 ppm HCl	Lifetime	Positive	Nasal squamous cell carcinoma	Sellakumar *et al.*, 1980a.
Formaldehyde	Rats, Fischer 344 mice, B6C3F1	2, 6, and 15 ppm	24 mo	Rats positive at 6 and 15 ppm; mice marginally positive at 15 ppm	Nasal squamous cell carcinoma	Swenburg *et al.*, 1980; Selikoff and Hammond, 1981.
Formaldehyde + HCl	Rats, Sprague–Dawley	14 ppm HCHO + 10 ppm HCl	Lifetime	Positive	Nasal squamous cell carcinoma	Albert *et al.*, 1982.
Formaldehyde	Hamsters, Syrian Golden	10 ppm	Lifetime	Negative	—	Dalbey, 1982.
Formaldehyde	Hamsters, Syrian Golden	30 pm once wkly + 5 mg DENA subcutaneously	Lifetime	Tumorigenic effect of DENA enhanced	Adenomas	Dalbey, 1982.
Furfural	Hamsters, Syrian Golden	250–400 ppm	12 mo	Negative	—	Feron and Kruysse, 1978.
HMPA	Rats, Sprague–Dawley	0.01–4 ppm	24 mo	Good dose-response curve	Nasal epidermoid carcinoma	Lee and Trochimowicz, 1982.

TABLE 1—*Continued*

Compound	Species and strain	Exposure levels	Duration of exposure	Response	Primary tumor type(s)	References
MC	Rats, Albino mice, Swiss Albino, C57BL	1.7 or 3.7 ppm 20 or 42 mg/m^3	9 mo	Negative	—	Kuschner *et al.*, 1957.
3-Nitro-3-hexene	Mice, Swiss Webster	0.2 ppm	15 mo	Positive	Lung adenocarcinoma	Deichmann *et al.*, 1963.
3-Nitro-3-hexene	Rats, CFN	1 and 2 ppm	36 mo	Positive	Lung anaplastic and squamous cell carcinoma	Anderson *et al.*, 1966.
Polyurethane dust	Hamsters, Syrian Golden rats, Sprague–Dawley	3.6 and 20 mg/m^3	40–43 days	Marginal increase in rats only	Lung squamous cell carcinoma	Laskin *et al.*, 1972.
Tetrachloro-ethylene	Rats, Sprague–Dawley	100 and 500 ppm	18 mo	Marginal increase in rats only	—	NCI, 1977.
Trichloro-ethylene	Rats, Sprague–Dawley hamsters, Syrian Golden mice, NMRI	100 and 500 ppm	18 mo	Negative except in female mice	Malignant lymphoma	Henschler *et al.*, 1980.
Trichloro-ethylene	Rats, Sprague–Dawley mice, B6C3F1	100, 300, and 600 ppm	24 mo	Negative for lung tumors; positive for liver tumors in rats	Hepatocellular carcinoma	Chu and Milman, 1981.
Urethane	Mice, BLH, NMRI, C57BL	Uncertain	Variable	Positive in as little as 7 wk	Pulmonary adenomas	Otto and Plotz, 1966.
Urethane	Mice, A/H	138 ppm	6.5 mo	Positive, very large response	Pulmonary adenomas	Leong *et al.*, 1971.
VB	Rats, Sprague–Dawley	10–1250 ppm	24 mo	Positive for several tumor types	Liver angiosarcoma; zymbal gland carcinoma	Benya *et al.*, 1982.
VC	Rats, Ar/IRE	30,000 ppm	12 mo	Positive for several tumor types	Lung adenocarcinoma; skin squamous cell carcinoma; liver angiosarcoma	Viola *et al.*, 1971.
VC	Rats, Ar/IRE rabbits	50–20,000 ppm, rats; 10,000 ppm, rabbits	12 mo	Positive for several tumor types	Skin acanthomas; lung adenocarcinomas	Caputo *et al.*, 1974.
VC	Rats, Sprague–Dawley	50–10,000 ppm	12 mo	Positive for a large variety of tumors; lung tumors not mentioned	Zymbal gland carcinoma; nephroblastoma; angiocarcinoma	Maltoni and Lefemine, 1975.
VC	Rats, Sprague–Dawley, Wistar	10,000 ppm	12 mo	Positive, Sprague–Dawley were more sensitive	Zymbal gland carcinoma; nephroblastoma; angiocarcinoma	Maltoni, 1977.
VC	Rats, Sprague–Dawley	6000 and 10,000 ppm	5 wk starting at 1 day or 13 wk of age	Positive only in rats starting exposure at 1 day of age	Zymbal gland carcinoma; nephroblastoma; angiocarcinoma	Maltoni, 1977.

TABLE 1—*Continued*

Compound	Species and strain	Exposure levels	Duration of exposure	Response	Primary tumor type(s)	References
VC	Hamsters, Syrian Golden mice, Swiss	50–10,000 ppm	7 mo	Positive	Pulmonary adenomas in mice; forestomach epithelial tumors in hamsters	Maltoni and Lefemine, 1975.
VC	Rats, mice, hamsters	1–30,000 ppm	5 wk–12 mo	A summary of all previous work	—	Maltoni *et al.*, 1981.
VC	Rats, Sprague–Dawley	50, 250, and 1000 ppm	12 mo	Positive at 2 higher dose levels	Liver angiosarcoma	Lee *et al.*, 1977.
VC	Rats, Sprague–Dawley	50, 250, and 1000 ppm	Up to 6 mo	Positive at 2 higher dose levels	Liver angiosarcoma	Hong *et al.*, 1981.
VC	Rats, Fischer 344	50–5000 ppm	1 hr	Negative	—	Hehir *et al.*, 1981.
VC	Rats, Sprague–Dawley	948 ppm	5.5 mo	Positive only among groups beginning exposure at 17 wk or less	Liver angiosarcoma	Groth *et al.*, 1981.
VC	Rats, Sprague–Dawley	600 ppm alone or with 5% ethanol in drinking water	12 mo	Positive with synergistic effects	Liver angiosarcoma	Radike *et al.*, 1981.

hamsters and 24 rats/group to either clean air or 6 ppm SO_2, 6 hr/day, 5 days/week for a lifetime. Twenty-one of the rats in each group and an unknown number of hamsters were exposed an additional hour each weekday to a combination of 10 mg/m^3 BaP + 3.5 ppm SO_2. No lung tumors were detected in the hamsters. Two of 21 rats exposed to BaP + SO_2 for 1 hr/day developed squamous cell carcinomas of the lung. Five of 21 exposed to SO_2 6 hr/day followed by BaP + SO_2 for an additional hour developed squamous cell carcinomas. No tumors were detected among the three remaining rats/group breathing clean air or SO_2 alone. Laskin *et al.* (1976) also reported results of a similar type of study using only rats. Separate groups were exposed to either clean air or 10 ppm SO_2, 6 hr/day, 5 days/week for a lifetime. Each of the two groups was further subdivided into three subgroups receiving no further exposure, 10 mg/m^3 BaP for an additional hour, or 10 mg/m^3 BaP + 4 ppm SO_2 for an additional hour. None of the rats exposed to clean air or SO_2 alone developed lung tumors. One of 30 exposed 1 hr/day to BaP and 2 of 30 exposed 6 hr/day to SO_2 + 1 hr/day to BaP developed squamous cell carcinoma of the lung. Four of 45 exposed 1 hr/day to BaP + SO_2 and 9 of 46 exposed 6 hr/day to SO_2 plus 1 hr/day to SO_2 + BaP developed lung tumors.

No neoplastic alterations were detected in Syrian hamsters exposed 4.5 hr/day, 5 days/week for up to 14 months to BaP at concentrations of 2, 10, 40, and 50 mg/m^3 (Mohr, 1978). Thyssen *et al.* (1981), on the other hand, were able to produce tumors in hamsters by condensing the BaP onto sodium chloride particles prior to inhalation. Twenty-four male Syrian Golden hamsters/group were exposed 4.5 hr/day, 7 days/week for the first 10 weeks and 3 hr/day, 7 days/week for the remainder of their lives to 2.2, 9.5, or 46.5 mg/m^3. No respiratory tract tumors were detected in controls or the low-dose group. An incidence of 35 and 52% was reported for the intermediate and high dose groups, respectively. Tumors were located in the nasal cavity, larynx, and trachea but none were found in the lungs.

Benzene. Snyder *et al.* (1980) exposed male AKR/J mice (50/group) and C57Bl/6J mice (40/group) 6 hr/day, 5 days/week for a lifetime to benzene, 100 ppm for AKR/Js and 300 ppm for C57Bls. Significant increases in tumor incidence were not detected in either strain.

Bis[chloromethyl]ether (BCME). Drew *et al.* (1975) and Laskin *et al.* (1971) exposed groups of 50 male Syrian Golden hamsters for 30, 10, 3, or 1 6-hr period to 1 ppm BCME. Only animals exposed three times or less survived more than 1 year. An early nasal esthesioneuroepithelioma was found 756 days after three exposures, and an unclassified malignant tumor was found in 1 animal dying 1000 days after a single exposure. Kuschner *et al.*(1975) exposed 100 hamsters to 0.1 ppm BCME 6 hr/day, 5 days/week for 16 weeks and then held them for a lifetime. Only one undifferentiated carcinoma of the lung was noted.

Exposure of A/H mice, 50/group, 6 hr/day, 5 days/week for 21 weeks to 1 ppm BCME resulted in a 55% tumor incidence with an average of 2.89 pulmonary adenomas/mouse (Leong *et al.*, 1971). This compared with a 41% tumor incidence and 0.87 tumors/mouse in controls held in clean air for 28 weeks. The earlier age at sacrifice of exposed mice along with a higher tumor incidence compared with controls was highly suggestive of a significant increase in exposed mice. Leong

et al. (1981) exposed 144–157 male HA/ICR mice/group, 6 hr/day, 5 days/week for 6 months to 100, 10, and 1 ppb BCME and observed them for a lifetime. Most of the animals died early as a result of ascending urinary tract infections. Of the mice surviving 7–24 months, the observed respiratory tumor incidence was 8/27, 3/37, 5/45, and 9/86 in the 100, 10, 1, and 0 ppb groups, respectively. A significant increase in tumor incidence ($P < 0.05$) was determined only for the 100-ppb group. The tumor types were all pulmonary adenomas or adenocarcinomas, with the exception of a lymphosarcoma in the nasal turbinates of one mouse in the high-dose group.

Although BCME produced some tumors in mice and hamsters, the rat was much more sensitive to the carcinogenic effects of this chemical. Kuschner *et al.* (1975) exposed male Sprague–Dawley rats 6 hr/day, 5 days/week to 0.1 ppm BCME. Groups of 50, 50, 20, 20, 30, and 30 were exposed for 2, 3, 8, 12, 16, and 20 weeks, respectively, and were held for a lifetime. The tumor incidence vs. length of exposure averaged 2.4%, 2 weeks; 6.5%, 4 weeks; 22.2%, 8 weeks; 22.2%, 12 weeks; 44.1%, 16 weeks; and 60%, 20 weeks. Of 40 respiratory tract tumors detected, 26 were in the nasal cavity and 14 were in the lungs. Thirteen of the lung cancers were classified as squamous cell carcinomas and one as an adenocarcinoma. Dulak and Snyder (1980) exposed an unspecified number of Sprague–Dawley rats to 0.1 ppm BCME, 6 hr/day, 5 days/week for 6 weeks and then held them for a lifetime. The data indicated that ≈35% of the animals would die with respiratory tract tumors. Leong *et al.* (1981) exposed 120 Sprague–Dawley SPF male rats/group, 6 hr/day, 5 days/week for 6 months to BCME at 100, 10, and 1 ppb and then observed them for a lifetime. Of the group exposed to 100 ppb, 86.5% of surviving animals developed nasal tumors (esthesioneuroepithelioma) and ≈4% developed pulmonary adenomas. An increased tumor incidence was not detected in rats exposed to 10 or 1 ppb.

Chloromethyl methylether (CMME). Laskin *et al.* (1975) exposed 90 hamsters 6 hr/day, 5 days/week for a lifetime to 1 ppm CMME; a single incidence of lung cancer was noted. In a similar experiment using male Sprague–Dawley rats (Drew *et al.*, 1975), only 1 squamous cell carcinoma of the lung and 1 nasal tumor was detected among 13 rats exposed to 1 ppm, 6 hr/day, 5 days/week for 6 weeks and held for a lifetime. Exposure of 50 A/H mice 6 hr/day, 5 days/week for 28 weeks to 2 ppm CMME resulted in a 50% tumor incidence with an average of 1.53 tumors/mouse. This compares with a 41% incidence and 0.87 tumor/mouse in controls, a difference of marginal significance (Leong *et al.*, 1971).

Diazomethane. Seven Porton-strain albino rats, 6 LAC 606 P male rats, 12 female A/2G mice, 12 male A/2G mice, and 8 male Swiss mice were exposed 1–3 min twice weekly for up to 6 months to an unspecified concentration of diazomethane (Schoental and Magee, 1962). Among 7 rats surviving more than 10 months, 2 developed pulmonary adenomas and 1 developed a squamous carcinoma. Seven of 10 exposed A/2G mice surviving for up to 10 months compared with 2 of 8 controls developed pulmonary adenomas. No tumors were detected in the male Swiss mice.

1,2-dibromo-3-chloropropane (DBCP). Reznik *et al.* (1980a) exposed 50 B6C3 mice of each sex 4 hr/day, 5 days/week for 103 weeks to either 0.6 or 3.0 ppm DBCP. None of the controls developed respiratory tract tumors. After 104 weeks,

tumors were detected in 13% of males and 87% of females exposed to 0.6 ppm and in 47% of males and 87% of females exposed to 3.0 ppm compared with none among controls. Tumor types included adenomas, squamous cell carcinomas, papillomas, carcinosarcomas, fibrosarcomas, and hemangiosarcomas. All originated in the nasal cavity. An identical study was also conducted using Fischer 344 rats (Reznik *et al.*, 1980b). Eighty-four percent of the males and 70% of the females exposed to 0.6 ppm as well as 93% of the males and 92% of the females exposed to 3.0 ppm developed nasal tumors. In the low-dose group the tumors were primarily benign, while in the high-dose group the majority were malignant. Most tumors were squamous cell papillomas, carcinomas, and adenocarcinomas.

Dichloroethylene (DCE) (also referred to as vinylidene chloride). As part of a larger study investigating effects of vinyl chloride, Lee *et al.* (1977) exposed 36 CD-1 mice and 36 CD albino rats of each sex to 55 ppm DCE 6 hr/day, 5 day/week for 12 months. No significant increase in lung tumor incidence was detected in either species, although three liver hemangiosarcomas were noted in mice and two in rats. Maltoni (1977) reported interim results of an ongoing study in which Swiss mice and Sprague–Dawley rats were exposed 4 hr/day, 4–5 days/week for 52 weeks to DCE and held for a lifetime. After 98 weeks, 25 of 300 mice exposed to 25 ppm developed kidney adenocarcinomas, compared with none in controls or in rats exposed to concentrations ranging up to 200 ppm DCE. In similar types of exposure, Maltoni *et al.* (1977b) also observed a significant ($P < 0.05$) increase in mammary tumors in female Swiss mice exposed to 25 ppm but not 10 ppm, and in Sprague–Dawley rats exposed to concentrations ranging from 10 to 150 ppm DCE. Finally, Hong *et al.* (1981) reported no increases in the tumor incidence in Charles River CD-1 mice or CD rats exposed 6 hr/day, 5 days/week for up to 10 months to 55 ppm DCE and held and additional 12 months.

Dimethylcarbamoylchloride (DMCC). Male Syrian Golden hamsters, 120/group were exposed 6 hr/day, 5 days/week for a lifetime to 1 ppm DMCC (Sellakumar *et al.*, 1980b). Of 99 exposed animals examined, 50 developed tumors. With the exception of a laryngeal papilloma, all were squamous cell carcinomas of the nasal cavity. An unknown number of rats were also exposed to 1 ppm DMCC 6 hr/day, 6 days/week for 5 weeks; 96% developed respiratory tract tumors during their lifetime. Dulak and Snyder (1980) reported that ≈35% of Sprague–Dawley rats exposed 6 hr/day for 30 exposures to 1 ppm DMCC died of unspecified respiratory tract tumors.

Dimethyl sulfate (DMS). Schlögel and Bannasch (1970) exposed Syrian hamsters, Wistar rats, and NMR mice to 0.5 ppm DMS, 6 hr/day, 5 days/week, either biweekly or twice weekly for 15 months and then observed them over 2.5 years. After examining 10 animals of each species, 6 nasal carcinomas, 3 lung carcinomas, 1 thoracic sarcoma, and 2 pulmonary adenomas were found.

Epichlorohydrin. Laskin *et al.* (1980) exposed 140 male Sprague–Dawley rats/group to 30 or 100 ppm epichlorohydrin 6 hr/day, 5 days/week for 6 weeks and held them for a lifetime. Fifteen animals in the high-exposure group and 2 in the low-exposure group developed squamous cell carcinomas of the nasal cavity. Even the small number of animals with tumors in the 30-ppm group was considered to be exposure-related because of the rarity of this tumor type among control animals.

Ethlylene dibromide (*EDB*). The National Cancer Institute (1981) recently reported the results of a carcinogenesis bioassay of EDB. Rats and mice of each sex were exposed to 10 or 40 ppm EDB 6 hr/day, 5 days/week for 78–103 weeks. A significantly increased incidence of nasal tumors was detected in both male and female rats at both exposure levels but not in mice. In an unpublished study by Wong *et al.*, rats were exposed 7 hr/day, 5 days/week for 18 months to 20 ppm EDB. Statistically significant increases in the incidence of both benign and malignant tumors of the spleen, mammary gland, and nasal cavity were reported.

Ethylene Oxide. In an unpublished study by Snellings *et al.*, Fischer 344 rats, 120/sex/group, were exposed 5 hr/day, 5 days/week for ≈2 years to 10, 30, or 100 ppm ethylene oxide. In the high-exposure group a significant increase in pancreatic adenomas, subcutaneous fibromas, peritoneal mesotheliomas, and mononuclear cell leukemia of the spleen was detected in males. Only leukemia was significantly increased in females.

Formaldehyde. Horton *et al.* (1963) exposed 60 C3H mice/group to 28 and 55 ppm formaldehyde 3 times weekly for 1 hr over a 35-week period. Another group was exposed to 27 ppm for 35 weeks and 83 ppm for an additional 35 weeks. No pulmonary tumors were detected in either of the exposure groups. An unspecified number of Sprague–Dawley rats were exposed to a combination of 14.6 ppm formaldehyde and 10.7 ppm HCl for a lifetime (Sellakumar *et al.*, 1980a). This combination of chemicals was used because of the possibility that they may react to form BCME. Twenty-five percent developed squamous cell carcinomas of the nasal cavity; the first tumor was observed at 305 days. The most detailed study to date involved exposure of Fischer 344 rats and B6C3F1 mice, 120/group/sex, 6 hr/day, 5 days/week for 24 months to 0, 2, 6, or 15 ppm formaldehyde. In a preliminary report 36 rats exposed to 15 ppm and 2 exposed to 6 ppm developed tumors after 15 months (Swenberg *et al.*, 1980). In a more recent update, 95 nasal cavity carcinomas were found in rats after 24 months exposure to 15 ppm and 3 after 24 months exposure to 6 ppm (Selikoff and Hammond, 1981). Two mice in the 15-ppm exposure group developed squamous cell carcinomas after 24 months. No tumors were detected in mice exposed to 0, 2, or 6 ppm or in rats exposed to 0 or 2 ppm.

Albert *et al.* (1982) exposed 8-week-old male Sprague–Dawley rats 6 hr/day, 5 days/week for a lifetime to a combination of 10 ppm HCl and 14 ppm formaldehyde premixed to maximize formation of BCME. Of 99 exposed animals, 25 developed squamous cell carcinomas and 3 papillomas of the nasal cavity compared with none in controls. In a second experiment using the same concentration of gases, 100 rats/group were exposed to either HCl or formaldehyde premixed as in experiment 1, not premixed, formaldehyde alone, HCl alone, or clean air. Preliminary results after 588 days exposure showed 12 nasal cancers in the premixed group, 6 in the not premixed group, 10 in the group exposed to formaldehyde alone, and none among rats exposed to HCl alone or to clean air.

Dalbey (1982) detected no tumors and only a minimal increase in hyperplastic and metaplastic areas in the nasal epithelium among 88 male Syrian Golden hamsters exposed to 10 ppm formaldehyde 5 hr/day, 5 days/week for a lifetime. In a second experiment, exposure of 50 animals/group to 30 ppm, 5 hr/day, 1 day/week for a lifetime also failed to induce respiratory tract tumors. However, treat-

ment with 10 weekly injections of diethylnitrosamine (DENA) 48 hr after formaldehyde inhalation resulted in a significantly larger ($P < 0.05$) number of pulmonary tumors/tumor-bearing animals compared with DENA treatment alone. No potentiating effects were noted if formaldehyde inhalation was begun after completion of the 10 DENA injections.

Furfural. Feron and Kryusse (1978) exposed Syrian Golden hamsters, 30/sex/group, 7 hr/day, 5 days/week to furfural vapor and held them an additional 29 weeks in clean air. Furfural concentration varied from 400 ppm initially to 250 ppm during the final 32 weeks of exposure. Separate groups were intratracheally instilled with either 18.2 or 36.4 mg BaP or subcutaneously injected with a total of 2.1 μl DENA. Furfural neither induced respiratory tract tumors nor enhanced the carcinogenicity of BaP or DENA.

Hexamethyl Phosphoramide (HMPA). Zapp (1975) exposed Charles River CD rats, 120 of each sex/group, 6 hr/day, 5 days/week to 0, 50, 400, or 4000 ppb HMPA. Of animals dying between the 6th and 8th month, 12 of 15 in the 4000 ppb group and 7 of 8 in the 400 ppb group had developed squamous cell carcinomas of the nasal cavity. More recently, Lee and Trochimowicz (1982) exposed male and female Charles River CD Sprague–Dawley rats to HMPA 6 hr/day for up to 24 months. The nasal tumor incidence among groups of 200–240 rats each exposed 24 months to 0, 10, 50, 100, 400, or 4000 ppb averaged 0, 20, 38, 82, and 83%, respectively. The first tumors appeared as early as 7 months at the highest dose. The predominant tumor types were epidermoid carcinomas (72%), adenoid squamous carcinomas (15%), and papillomas (8%).

Methylcholanthrene (MC). Kuschner *et al.* (1957) exposed albino rats, Swiss albino mice, and C57BL mice to either 20 or 42 mg/m^3 MC 1 hr/day, 5 days/week. Exposures lasted up to 267 days and animals were held up to 772 days of age. Six of 69 Swiss mice but none of the 75 rats or 56 C57BL mice exposed to an aerosol of 42 mg/m^3 MC in corn oil developed tumors. None of 120 Swiss mice or 33 rats exposed to an aerosol of 20 mg/m^3 MC in saline developed respiratory tract tumors.

3-nitro-3-hexene. Deichman *et al.* (1963) exposed 20 Swiss Webster mice of each sex 6 hr/day, 5 days/week for 15 months to 0.2 ppm 3-nitro-3-hexene. Adenocarcinomas of the lung were found in 2 males and 3 females. One pulmonary adenoma was found in controls. In a followup study using 100 CFN rats/group exposed 6 hr/day for 36 months, 6 animals exposed to 1 ppm and 11 exposed to 2 ppm developed malignant lung tumors compared with none in controls. The tumors were anaplastic and squamous cell carcinomas (Anderson *et al.*, 1966).

Polyurethane. Laskin *et al.* (1972) exposed male Sprague–Dawley rats and male Syrian hamsters to 3.6 or 20 mg/m^3 polyurethane dust 6 hr/day, 5 days/week for 40–43 days and then held them for a lifetime. One of 39 rats exposed to the low dose and 1 of 45 exposed to the high dose developed squamous cell carcinoma of the lungs. None of 40 hamsters exposed to the low dose or 50 exposed to the high dose developed respiratory tract cancer.

Tetrachloroethylene. NCI (1977) conducted a bioassay to assess the carcinogenicity of tetrachloroethylene (or perchloroethylene). Sprague–Dawley rats, 96 of each sex, were exposed 7 hr/day, 5 days/week for 135 weeks to 0, 300, or 600 ppm. No increase in tumor incidence was reported.

Trichloroethylene (TCE). Exposure of NMRI mice, Wistar rats, and Syrian hamsters, 30/group of each sex, 6 hr/day, 5 days/week for 18 months to 0, 100, and 500 ppm TCE generally failed to produce an increase in tumor incidence. The one exception was an increase in the incidence of malignant lymphomas in female mice (Henschler *et al.*, 1980). In an unpublished report reviewed by Chu and Milman (1981), B6C3F1 mice and Charles River Sprague–Dawley rats, 100 of each sex/group, were exposed for 104 weeks to 1, 100, 300, or 600 ppm TCE. Among mice, the percentage with hepatocellular carcinomas averaged 12.1, 16.4, 20.6, and 28.5 after exposure to 1, 100, 300, and 600 ppm, respectively. The incidence of tumors in rats was not given, but TCE was reported as noncarcinogenic in this species.

Urethane. Otto and Plotz (1966) exposed 101 BLH, 123 NMRI, and 48 C57BL mice to urethane aerosols containing 5–20% NaCl for 20–60 min/day. All three strains developed pulmonary adenomas in as little as 7 weeks of exposure. While the BLH and NMRI only developed adenomas, the C57BL had mostly tumors of a solid type. Leong *et al.* (1971) exposed A/H mice, 50/group, 6 hr/day, 5 days/week for 28 weeks to either clean air or 138 ppm urethane. Tumors were detected in 94% of exposed mice with an average of 54.2 tumors/mouse compared to a 41% incidence and 0.87 tumor/mouse in controls.

Vinyl Bromide (VB). The inhalation carcinogenicity of VB was studied by Benya *et al.* (1982). One hundred and twenty 9- to 10-week-old Sprague–Dawley rats of each sex/group were exposed 6 hr/day, 5 days/week for up to 24 months to 10, 50, 250, or 1250 ppm VB. Due to excessive mortality, the group exposed to 1250 ppm was terminated at 18 months. Liver angiosarcomas increased in a clearcut, highly significant ($P < 0.001$), dose-related manner in both males and females from a total of 1 for both sexes breathing clean air to 122 at 250 ppm. Zymbal gland carcinomas also showed a significant ($P < 0.005$) increase in males exposed to 250 and 1250 ppm and in females exposed to 1250 ppm ($P < 0.001$). Hepatocellular carcinoma and liver neoplastic nodules showed significant but not dose-related increases in females only.

Vinyl Chloride (VC). The carcinogenic action of VC was first reported by Viola *et al.* (1971). Of 26 male Wistar AR/IRE rats exposed 4 hr/day, 5 days/week for 12 months to 30,000 ppm VC, 6 developed bone tumors, 15 developed skin tumors, and 6 developed lung tumors (1 squamous cell and 5 adenocarcinomas). This was followed up by a larger study in which groups of 150–200 Wistar AR/IRE rats comprised of both males and females were exposed 5 hr/day, 5 days/week for 12 months to 50, 500, 2000, 5000, 10,000, or 20,000 ppm VC (Caputo *et al.*, 1974). Highly significant increases in cancer incidence ($P < 0.01$) to ($P < 0.005$), were detected in every exposure group except 50 ppm where no tumors were detected. Skin squamous cell carcinoma, lung adenocarcinoma, and liver angiosarcoma were the most common types found. The incidence of lung tumors was 21/150 at 20,000 ppm. In rabbits exposed under similar conditions to 10,000 ppm, skin acanthomas were detected in 12/40 and lung adenocarcinomas in 6/40 compared with none in controls.

Maltoni and Lefemine (1975) conducted a large number of inhalation exposures to VC. In the first of this series, both male and female Sprague–Dawley rats, 68–74 group, were exposed 4 hr/day, 5 days/week for 12 months to 50, 250, 500,

2500, 6000, or 10,000 ppm VC and then held in clean air for an additional 19 months. The numbers of rats with any tumor types averaged 10% for controls, 17% at 50 ppm, 27% at 250 ppm, 37% at 500 ppm, 54% at 2500 ppm, 52% at 6000 ppm, and 62% at 10,000 ppm. The more common tumor types included Zymbal gland carcinomas, nephroblastomas, liver angiosarcomas, subcutaneous angiomas, hepatomas, and brain neuroblastomas. Lung tumors were not mentioned. Swiss mice (30 males, 30 females/group) were also exposed for 30 weeks under the same conditions as the rats and sacrificed 11 weeks postexposure. Pulmonary adenomas were the primary tumor type with an incidence of 0.7% in controls compared with 14% at 50 ppm, 26% at 250 ppm, 29% at 500 ppm, 25% at 2500 ppm, 50% at 6000 ppm, and 56% at 10,000 ppm VC. Syrian hamsters exposed identically showed no significant increase in tumor incidence after 28 weeks exposure.

Maltoni (1977) showed that Sprague–Dawley rats were much more sensitive than Wistar rats to the induction of Zymbal gland (ear canal) tumors. Following exposure to 10,000 ppm 4 hr/day, 4–5 days/week for 52 weeks, 10 of 30 male Sprague–Dawley vs. 1 of 30 Wistar rats developed Zymbal gland tumors. Early exposure was also shown to be important. Among male Sprague–Dawley rats exposed 4 hr/day, 5 days/week to 6000 and 10,000 ppm VC for 5 weeks and held an additional 135 weeks, 48 of 89 exposed starting at 1 day of age vs. 1 of 240 that began exposure at 13 weeks developed liver tumors.

In an update of continuing studies, Maltoni (1978) reported that significant increases also occurred in Syrian hamsters exposed to VC. As was true with mice and rats, the dose–response curve was relatively flat despite the wide range of doses. For example, 12 of 33 exposed to 50 ppm compared with 13 of 35 exposed to 10,000 ppm developed tumors. Similar to results with rats, very few lung tumors were reported.

Maltoni *et al.* (1981) summarized all their experiments over the past 10 years. During this period over 7000 animals were exposed to 28 combinations of exposure time and concentration. The majority were exposed 4 hr/day, 5 days/week for 52 weeks to 14 concentrations of VC ranging from 1 to 30,000 ppm. Among these groups the dose–response curve averaging all malignant tumors was relatively shallow with a mean, in rats, of about 1 tumor/animal exposed to 30,000 ppm compared with 0.25 tumor/animal breathing clean air. The most common tumor types were liver angiosarcomas, Zymbal gland carcinomas, and mammary tumors. While the first two types were predominant at high concentrations of VC, the greatest number of mammary tumors occurred in the 1–50 ppm dose range. This unusual tumor distribution is part of the reason for the shallow dose–response curve. Other tumor types which were significantly increased in at least one experiment were nephroblastomas, neuroblastomas, and forestomach papillomas.

Lee *et al.* (1977) exposed Charles River CD rats, 36 of each sex/group, 6 hr/day, 5 days/week for 12 months to 0 50, 250, or 1000 ppm VC. Twenty-one of the rats exposed to 1000 ppm, 10 exposed to 250 ppm, and 2 exposed to 50 ppm died during exposures. A significant increase in tumor incidence was detected at the two highest doses with liver hemangiosarcomas predominating. Only a few lung tumors were reported. In a sequel to this study 4 to 16 Charles River CD

rats of each sex/group were exposed under the same conditions except that the exposure duration was shortened to 1, 3, 6, or 10 months, followed by a 12-month holding period (Hong *et al.*, 1981). Cumulative tumor incidence increased with both concentration and exposure duration. Although 15 mammary gland tumors were detected in the 50 ppm groups, differences from controls were not considered significant. At 250 ppm, significant increases were detected only at the longer exposure durations. Liver hemangiosarcomas and hepatocellular carcinomas were most common and the only ones showing a significant increase at any concentration. Lung cancer was detected in 15 of 206 rats exposed 6 or 10 months compared with none among 72 controls.

Hehir *et al.* (1981) conducted studies designed to evaluate the hazards of high-level, short-term exposures such as might occur in industrial accidents. No increases in tumor incidence were detected among 85–100 Fischer 344 rats of each sex/group exposed for 1 hr to 50, 500, 5000, or 50,000 ppm VC and held for a lifetime. Likewise, no increases in tumor incidence were detected in additional groups exposed 1 hr/day, 5 days/week for either 2 weeks to 500 ppm or 20 weeks to 50 ppm.

Another study by Groth *et al.* (1981) was designed to evaluate the influence of age upon susceptibility to the carcinogenic effects of VC. Sprague–Dawley rats, 110–128/group/sex, were exposed 7 hr/day, 5 days/week for 24 weeks to 948 ppm VC and the majority held for 43 weeks postexposure. Four groups averaging 6, 17–18, 32–33, and 51–53 weeks of age at the start of exposure were used. Among males the incidence of liver angiosarcomas averaged 0, 0, 6, and 24% in the oldest to youngest age groups, respectively. Similarly, females averaged 5.3, 15, 47, and 20%. Radike *et al.* (1981) studied the influence of ethanol upon susceptibility to VC inhalation. Male Sprague–Dawley rats, 80/group, were exposed 4 hr/day, 5 days/week for 12 months to either 600 ppm VC alone or in combination with 5% ethanol in the drinking water. Liver angiosarcomas were detected in 50% of the combined-exposure group compared with 23% in rats exposed to VC alone and none in controls or ethanol-treated animals. Ethanol treatment alone, however, resulted in a high incidence of nonhepatic tumors. Lung tumor incidence was not reported.

The VC experiments described thus far involved mainly rats which were relatively resistant to lung tumor induction by VC. The mouse, on the other hand, appears to be more sensitive. In the studies by Maltoni *et al.* (1981), an experiment using Swiss mice, 56–60/sex/group, exposed 4 hr/day, 5 days/week for 38 weeks to 50, 250, 500, 2500, 6000, and 10,000 ppm was included. After 81 weeks lung tumors were the predominant form of cancer with an incidence of 57–87% in both males and females exposed to 250 ppm or more. The incidence in both the controls and 50 ppm groups averaged about 10%. The lung tumor types were not listed. Keplinger *et al.* (1975) exposed Charles River COBS rats, CD-1 Swiss mice, and Syrian Golden hamsters, 100/species/sex, 7 hr/day, 5 days/week for 9 months to 0, 50, 200, and 2500 ppm VC followed by a 9-month holding period. Interim results were presented only for mice dying within 8 months from the start of exposure. The incidence of tumors averaged 0, 4, 13, and 30% for the low- to high-exposure groups, respectively; pulmonary adenomas and liver angiosarcomas were most common and present in about equal numbers.

In a study described earlier by Lee *et al.* (1977), CD-1 mice as well as rats were exposed to 50, 250, or 1000 ppm VC. Of the mice exposed to 250 and 1000 ppm, only 1 survived as long as 12 months. Pulmonary adenomas occurred as early as the second month of exposure and were present in nearly all mice that died during exposure. Hemangiosarcomas occurred as early as the sixth month of exposure. A clear-cut dose–response curve could be seen for lung tumors, liver hemangiosarcomas, and mammary tumors. In a followup study by Hong *et al.* (1981) using the same exposure conditions, similar results were reported.

Suzuki (1978) exposed 27 male Charles River CD-1 mice, 4–5 weeks of age, 5 hr/day, 5 days/week for 5 or 6 months to either 2500 or 6000 ppm VC followed by a holding period of up to 37 days. Pulmonary adenomas were found in 26 of 27 mice. In a followup study, 9 male CD-1 mice/group were exposed as above for 4 weeks to 0, 1, 10, or 100 ppm VC and sacrificed 40 weeks later (Suzuki, 1981). Pulmonary adenomas were detected even after this short exposure period with tumors detected in 0 of 10, 1 of 9, 2 of 9, and 5 of 9 mice exposed to 0, 1, 10, and 100 ppm VC, respectively. A/J mice, 90/sex/group, were also exposed 1 hr/day, 5 days/week for either 2 weeks to 500 ppm or 20 weeks to 50 ppm and held for 20 months. The incidence of pulmonary adenomas averaged 75% in the 500 ppm group vs. 35% for controls ($P < 0.01$). A 41% incidence in the 50 ppm group was not significantly greater than controls even though the total exposure was comparable to the 500 ppm group.

Several conclusions can be drawn from the large number of inhalation studies conducted using VC. First of all, the primary tumor types found in the rat were liver angiosarcomas and hepatocellular carcinomas followed by Zymbal gland and mammary gland tumors. Few investigators reported lung tumors in the rat. In the mouse, on the other hand, pulmonary adenomas predominated, although liver and mammary cancer developed in the animals that survived for a long enough period. The overall slope of the dose–response curve for rats was small. This overall response was complicated by the fact that mammary tumors showed a high incidence only at low concentrations; certain other types, such as those of the Zymbal gland, developed at much higher concentrations. It is also noteworthy that in all studies in which mice and rats were both used, the mouse was much more sensitive to VC toxicity. According to Ramsey and Gehring (1980), this is due to the rapid metabolism of such compounds by mice.

A final, somewhat disturbing note is the wide range of susceptibility to the toxic effects of VC reported by different investigators. Viola *et al.* (1971) obtained good survival of rats exposed to 30,000 ppm; Maltoni and Lefemine (1975) obtained satisfactory survival in mice exposed to 10,000 ppm. Lee *et al.* (1977), on the other hand, reported a loss of almost all mice exposed to 250 and 1000 ppm. The reasons for these differences in susceptibility is unknown but could be related to impurities present.

IV. INORGANIC METALLIC COMPOUNDS

Results of studies discussed in this section are summarized in Table 2.

Antimony (Sb). Twenty male Sprague–Dawley rats were exposed ≈25 hr/week for 12.5–14 months to antimony trioxide (Sb_2O_3) (mean particle size 0.6 μm) at a concentration of 100–125 mg/m^3 (Gross *et al.*, 1952). Although the exposures produced definite indications of lipoid pneumonia, none of the rats developed lung cancer.

TABLE 2

ONCOGENIC RESPONSES FROM INHALATION OF METALLIC COMPOUNDS[a]

Compound	Species and strain	Exposure levels	Duration of exposure	Response	Primary tumor type(s)	References
Antimony trioxide	Rats, Sprague–Dawley	100–125 mg/m³	12.5–14 mo	Negative	—	Gross *et al.*, 1952.
Beryllium sulfate	Rats, Sherman Wistar	0.035 mg/m³	6 mo	Positive	Adenocarcinomas; adenomas	Schepers *et al.*, 1957a.
Beryllium sulfate	Rats	0.64 mg/m³	Up to a lifetime	Positive	Adenomas	Vorwald and Reeves, 1959; Vorwald, 1953.
Beryllium oxide	Rats	0.05 mg/m³	Up to a lifetime	Positive	Adenomas	Vorwald and Reeves, 1959; Vorwald, 1953.
Zinc manganese beryllium silicate	Rats	20 and 31 mg/m³	6–8 mo	Positive	Adenomas; adenocarcinomas	Schepers, 1961.
Beryllium fluoride	Rats	.048 mg/m³	6–15 mo	Positive	Adenomas; adenocarcinomas	Schepers, 1961.
Beryllium phosphate	Rats	3.9 and 26 mg/m³	6 mo	Positive	Adenomas; adenocarcinomas	Schepers, 1961.
Beryllium oxide	Rats	28 mg/m³	1 mo	Negative	—	Schepers, 1961.
Beryllium sulfate	Rats	0.003, 0.021 0.048 mg/m³ as Be	18 mo	Positive in all groups; almost 100% in high dose group	Adenomas; squamous cell carcinoma	Vorwald *et al.*, 1966.
Beryllium sulfate	Rats, Sprague–Dawley	0.034 mg/m³ as Be	13 mo	100% incidence	Adenocarcinomas	Reeves *et al.*, 1967.
Beryl	Rats, Sprague–Dawley hamsters, Syrian Golden	15 mg/m³	Up to 23 mo	Positive for beryl only	Adenocarcinomas	Wagner *et al.*, 1969.
Bertrandite	Rats, Sprague–Dawley	15 mg/m³	Up to 23 mo	Negative	—	Wagner *et al.*, 1969.
Chromate dust	Rats, Wistar, McCollum mice, A, Swiss, C57BL	2–3 mg/m³	Up to 13 mo for mice; up to 23 mo for rats	Small but significant increase in rats; negative in mice	Lymphosarcomas	Baetjer *et al.*, 1959.
Chromate dust	Mice, C57BL	25 mg/m³ alone or after infection with influenza virus	Lifetime	Negative	—	Nettesheim *et al.*, 1970, 1971.
Cobalt oxide	Hamsters, Syrian Golden ENG:FLA	10 mg/m³ alone or with cigarette smoke	Lifetime	Negative	—	Wehner *et al.*, 1977a.
Nickel dust	Mice	Not reported	Lifetime	An increase of borderline significance	—	Campbell, 1943.

TABLE 2—*Continued*

Compound	Species and strain	Exposure levels	Duration of exposure	Response	Primary tumor type(s)	References
Nickel dust	Rats, Wistar, Bethesda Black, mice, C57BL, guinea pigs	15 mg/m³	Up to 21 mo	Positive for rats only	Pulmonary adenomas	Hueper, 1958.
Nickel dust + limestone + SO_2	Rats, Bethesda Black hamsters, Syrian Golden	Not reported	Up to 24 mo	Negative	—	Hueper and Payne, 1962.
Nickel carbonyl	Rats, Wistar	30 and 60 mg/m³	12 mo	Small increases; significance not reported	Adenocarcinomas	Sunderman *et al.*, 1959.
Nickel carbonyl	Rats, Wistar	30 mg/m³	Lifetime	Small but probably significant increases	Adenocarcinomas	Sunderman, 1966; Sunderman and Donnelly, 1965.
Nickel sulfide	Rats, Fischer 344	1 mg/m³	18 mo	Positive	Adenomas; adenocarcinomas	Ottolenghi, 1975.
Nickel oxide alone or with cigarette smoke	Hamsters, Syrian Golden ENG:FLA	0.053 mg/m³	Lifetime	Negative	—	Wehner *et al.*, 1975.
Nickel-enriched fly ash	Hamsters, Syrian Golden LAK:LVG	75 mg/m³ (20% Ni)	Up to 20 mo	Negative	—	Wehner, 1980.
Titanium dust	Rats, Wistar	10–328 million particles/cu ft	Up to 13 mo	Negative	—	Christie *et al.*, 1963.

[a] Results of a large number of exposures to a variety of beryllium compounds by Schepers *et al.*, 1971 are listed in Table 3.

Beryllium (Be). Schepers *et al.* (1957a) exposed 136 rats (21 Sherman, 115 Wistar), of which about one-half were females, 8 hr/day, 5.5 days/week for 6 months to beryllium sulfate at a beryllium concentration of 35 $\mu g/m^3$. Fifty-two survivors were held in clean air for up to an additional 18 months. Seventy-six pulmonary neoplasms were detected including 24 acinous adenocarinomas, 11 papillary adenocarcinomas, 7 alveolar cell adenocarcinomas, 18 adenomas, 7 mucigenous tumors, 5 squamous carcinomas, 1 endothelioma, and 1 retesarcoma. No lung tumors were detected in 139 controls. Vorwald and Reeves (1959) and Vorwald (1953) exposed rats 6 hr/day, 5 days/week to beryllium sulfate or oxide for up to a lifetime. The beryllium concentration in the chambers averaged 0.64 mg/m^3 for the sulfate and 0.05 mg/m^3 for the oxide. Tumor induction was found, but the numbers were not reported. The tumors were usually adenomatous, but some epidermoid and squamous types were present.

Schepers (1961) reported tumor incidences in rats exposed for an unreported number of hours/day to a variety of beryllium compounds. ZnMnBe silicate (20 mg/m^3) resulted in an 8% incidence of tumors by 8 months. A second group exposed to 31 mg/m^3 ZnMnBe silicate for 6 months and held in room air for an additional 6 months developed a 30% incidence of lung tumors. Among groups of 100 exposed to 48 $\mu g/m^3$ BeF for 6, 12, or 15 months, the tumor incidence averaged 3, 4, and 8% for the three groups, respectively, 15 months from the start of exposure. Among 135 rats exposed to $BeHPO_4$ (3.9 mg/m^3) for 6 months and held an additional 6 months, a 35% incidence of lung cancer was found. Another group of 40 exposed for 1 month to 26 mg/m^3 $BeHPO_4$ and held an additional 9 months developed an 18% incidence of lung tumors. Exposure to BeO (28 mg/m^3) for 12 months did not result in lung tumor induction.

Vorwald *et al.* (1966) exposed rats to beryllium sulfate aerosols 7 hr/day, 5 days/week for 18 months at beryllium concentrations of either 42 or 21 $\mu g/m^3$. Lung cancer was detected as early as the ninth month of exposure. The lung cancer incidence in a large number surviving 18 months was almost 100%. In an additional group exposed to 2.8 $\mu g/m^3$, 13 of 21 rats surviving for 18 months developed lung cancer. The predominant pathology was usually adenomatous, but epidermoid and squamous cell carcinomas also occurred. Reeves *et al.* (1967) exposed Charles River, Sprague–Dawley CD rats, 75 of each sex/group, to beryllium sulfate at a beryllium concentration of 34 $\mu g/m^3$, 7 hr/day, 5 days/week. The first appearance of lung tumors was detected after 9 months of exposure with the incidence reaching 100% by 13 months. The tumors were all adenocarcinomas of apparently alveolar origin. Wagner *et al.* (1969) exposed 93 male Charles River CR-CD rats, 30 male Greenacres controlled Flora (GA) rats, and 65 male Syrian Golden hamsters/group to either beryl or bertrandite (beryllium-containing ores), 6 hr/day, 5 days/week for up to 17 months. The concentrations of both ores were maintained at 15 mg/m^3 resulting in a beryllium concentration of 210 $\mu g/m^3$ in the bertrandite chambers and 620 $\mu g/m^3$ in the beryl chambers. Five of 11 rats exposed to beryl developed small foci of squamous metaplasia or tiny epidermoid tumors within 12 months. By 17 months, 18 of 19 animals remaining had developed tumors. The primary tumor types appeared to be of bronchoalveolar origins. Seven were classified as adenoma and 9 as adenocarci-

nomas. No tumors were detected in rats exposed to bertrandite or in hamsters exposed to either ore. This incidence was considered significant because of the historic lack of lung cancer in controls.

Schepers (1971) exposed rats for 15 months and guinea pigs and rabbits for 12 months to a variety of beryllium compounds alone or in combination with other airborne pollutants. The breed/sex of the animals and details of the exposure regime were not given. No lung tumors were detected among 210 rats, 10 rabbits, or 48 guinea pigs held in clean air. The lung tumor incidence in the exposed animals is listed in Table 3. In general, as was true in earlier studies, the carcinogenicity of beryllium was closely related to the solubility of the compound used.

Chromium. Baetjer *et al.* (1959) exposed both male and female Strain A mice, Swiss mice, C57B1 mice, and mixed Wistar and McCollum rats 4 hr/day, 5 days/week to chromate dust. Rats were exposed up to 101 weeks to a concentration of 2–3 mg/m^3, and mice were exposed up to 46 weeks for Strain A and up to 58 weeks for the other strains to 1–2 mg/m^3. The incidence of pulmonary adenomas in the mice was not significantly increased. Four lymphosarcomas were detected in 100 exposed rats compared with 2 in 391 controls. Although the difference was statistically significant, the authors considered it only suggestive because such neoplasms are relatively common in rats. Nettesheim *et al.* (1970, 1971) exposed 545 C57B1 mice/group, one-half of each sex, 5.5 hr/day, 5 days/week for a lifetime to either clean air or chromate dust at a concentration of 25 mg/m^3. One-half of

TABLE 3
TUMOR INDUCTION IN ANIMALS EXPOSED TO A VARIETY OF BERYLLIUM COMPOUNDS[a]

Aerosol composition	Species	Concentration of beryllium compounds (mg/m^3)	Number exposed	Percentage with lung tumors
BeF_2	Rat	2.81	180	36
BeO + quartz	Rat	20.2	36	31
Zn Mn Be Sil	Rat	20.7	230	30
$BeSO_4$ + Fe_2O_3	Rat	0.34	36	25
Be HPO_4	Rat	21.3	240	16
$BeSO_4$	Rat	0.34	240	16
$BeSO_4$ + chrysotile	Rat	20.2	40	10
BeO (milled)	Rat	20.2	20	0
BeO (high fired)	Rat	20.2	36	0
BeO + fiberglass	Rat	20.2	24	0
BeO + sil	Rat	20.2	20	0
BeO + cort	Rat	20.2	20	0
Zn Be Mn sil + fiberglass	Rat	20.7	20	0
$BeSO_4$	Guinea pig	0.34	20	10
BeO (milled)	Guinea pig	20.2	20	5.0
BeO (fluorescent grade)	Guinea pig	20.2	20	3.3
Zn Mn Be Sil	Guinea pig	20.7	30	0
Zn Mn Be Sil	Rabbit	20.7	20	15.0

[a] Schepers, 1971.

the mice in each group were infected with PR-8 influenza virus 2 weeks prior to the start of inhalation exposure. In the non-virus-treated mice, 5 clean air vs. 7 chromate-exposed mice developed lung tumors; none of the clean air vs. 8 of the chromate-exposed mice pretreated with virus developed tumors. Laskin (1973) reported interim results for rats and hamsters chronically exposed to 2 mg/m^3 Ca chromate. At the time of the report, one squamous cell carcinoma of the lung and one of the larynx was seen in the rats, along with one squamous cell carcinoma of the larynx in hamsters. Unfortunately, details of the exposure conditions were not given.

Cobalt. Wehner *et al.* (1977a) exposed 51 male ENG:ELA Syrian hamsters/group, 7 hr/day, 5 days/week to Cobalt oxide, 10 mg/m^3; cigarette smoke 3 times daily, 5 days/week; or both in combination for a lifetime. Neither treatment alone or in combination resulted in any increase in lung tumor incidence.

Nickel. The earliest work relating to inhalation of nickel was done by Campbell (1943). Mice were exposed 5 days/week for a lifetime to an unspecified concentration of nickel dust. Lung tumors were detected in 29.5% of exposed mice compared with 12.5% of controls, a difference the author considered to be of borderline significance. Hueper (1958) exposed 32 male and 10 female guinea pigs, 50 Wistar rats of each sex, 60 female Bethesda Black rats, and 20 female C57B1 mice 6 hr/day, 5 days/week for up to 21 months to 15 mg/m^3 nickel dust. Of 50 rats examined, 15 developed pulmonary adenomas but no nasal tumors. An intraalveolar tumor was noted in 1 of 42 guinea pigs, and multiple pulmonary adenomas were found in another. No tumors were detected in mice or in controls. Hueper and Payne (1962) exposed 27 Bethesda Black rats and 14 Syrian hamsters of an unreported sex 5–6 hr/day for up to 24 months to a mixture of nickel dust limestone, and SO_2 of uncertain concentration. No malignant lung tumors were detected in either species.

The carcinogenicity of nickel carbonyl was first investigated by Sunderman *et al.* (1959). Male Wistar rats were exposed 30 min/day, 3 days/week for 1 year to either 30 or 60 mg/m^3 nickel carbonyl and held for a lifetime. Another group was exposed for one 30-min period to 250 mg/m^3, an LD_{50} dose, and held for a lifetime. Survival rates after 2 years were 3/41, 5/63, 1/30, and 3/80 for the controls and the 30, 60, and 250 mg groups, respectively. One rat from each chronic exposure group and two from the single exposure developed lung tumors. Two were adenocarcinomas, 1 was a squamous cell tumor, and 1 was a papillary adenoma. Sunderman (1966) and Sunderman and Donnelly (1965) exposed 64 male Wistar rats to nickel carbonyl at 30 mg/m^3. The study was similar to the previous one except the animals were exposed for a lifetime. An adenocarcinoma was reported in one exposed animal and a squamous cell carcinoma of the salivary gland in another, compared with none in controls. This incidence was considered significant because of the historic lack of lung cancer in controls.

Nickel sulfide carcinogenesis was studied by Ottolenghi *et al.* (1975). Fisher 344 rats, 122 males and 104 females, were exposed 6 hr/day, 5 days/week for 78 weeks to nickel sulfide at a concentration of 1 mg/m^3 followed by an additional 30 weeks holding period. The overall lung tumor incidence averaged 14% compared with 1% in controls. The tumor types included 15 adenomas, 10 adenocarcinomas, 3 squamous cell carcinomas, and 1 fibrosarcoma.

Wehner *et al.* (1975b) investigated the effects of nickel oxide and cigarette smoke in combination upon lung cancer. Male Syrian golden hamsters, 51/group, were exposed 7 hr/day, 5 days/week to 53 $\mu g/m^3$ nickel oxide; cigarette smoke exposure three times daily; or both in combination for a lifetime. Neither treatment alone, or in combination resulted in lung tumor development. Negative results were also obtained in a study in which 102 male LAK:LVG hamsters/group were exposed 6 hr/day, 5 days/week for up to 20 months to either ordinary fly ash (0.03% Ni) or fly ash enriched with nickel (20% Ni). Maximum concentrations used were 75 mg/m^3 (Wehner, 1980).

Titanium. Christie *et al.* (1963) exposed 23 male Wistar rats to titanium dust for up to 13 months and held them for an additional 20 months. Dust was generated four times daily resulting in 10–328 million particles/ft^3. No lung tumors were detected.

V. INORGANIC NONMETALLIC COMPOUNDS

Results of studies discussed in this section are summarized in Table 4.

Asbestos. Vorwald *et al.* (1951) summarized a series of studies in which guinea pigs, rabbits, cats, and rats were exposed up to 42 months to various types of asbestos dust. Concentrations were given in dust counts which were usually near 3.5 billion/m^3. No evidence for lung cancer was detected among hundreds of exposed animals. Lynch *et al.* (1957) exposed A/C F_1 mice to asbestos dust 5 days/week, 8–12 hr/day for a lifetime at a particle count of 5.3–10.5 billion/m^3. Among females the lung tumor incidence averaged 27% (32/119) in controls vs. 36% (23/64) in exposed mice. Among males, 37% (38/103) for controls vs. 55% (35/64) exposed developed lung tumors. Combining data from males and females resulted in differences of borderline significance ($P < 0.07$). When the incidence of multiple tumors was compared the results were highly significant ($P < 0.01$).

Gross *et al.* (1967) exposed 131 male rats 6 hr/day, 5 days/week for up to 62 weeks to chrysotile dust at concentrations varying from 42 to 146 mg/m^3. Seventy of the group were pretreated with an intratracheal instillation of 0.05 ml, 5% NaOH. Of 31 asbestos-exposed, instilled rats surviving 16 months, 15 developed lung tumors, along with 10 of 41 noninstilled survivors. None of 40 clean air controls or 15 instilled with NaOH and breathing clean air developed lung tumors. The tumor types included 20 adenocarcinomas, 4 squamous cell carcinomas, 6 fibrosarcomas, 1 mesothelioma, and 4 adenomas. Reeves *et al.* (1971) exposed rats, rabbits, guinea pigs, and hamsters, 32–77/species/group to amosite, crocidolite, or chrysotile at a concentration of 48 mg/m^3, 4 hr/day, 4 days/week for up to 24 months. The only tumors detected were two pulmonary carcinomas in rats exposed to crocidolite. In a followup study, Reeves *et al.* (1974) divided 108 Cam-Hartly guinea pigs, 72 Dutch rabbits, 216 Mongolian gerbils, 100 Swiss mice, and 219 Charles River CD rats among 4 groups and exposed them to clean air or to amosite, crocidolite, or chrysotile at a mean concentration of 48–50 mg/m^3. The animals were exposed 4 hr/day, 4 days/week for up to 2 years. None of the mice survived as long as 18 months. The only lung tumors detected were in rats, with 7 lung carcinomas and 3 mesotheliomas, representing a 7–9% malignancy rate among animals with an adequate survival record. Three of the tumors were in

TABLE 4
ONCOGENIC RESPONSES FROM INHALATION OF NONMETALLIC INORGANIC COMPOUNDS

Compound	Species and strain	Exposure levels	Duration of exposure	Response	Primary tumor type(s)	References
Asbestos	Cats, rats, rabbits, Guinea pigs	≈3.5 billion particles/m³	Up to 42 mo	Negative	—	Vorwald *et al.*, 1951.
Asbestos	Mice: A/C F1	5.3–10.5 billion particles/m³	Lifetime	Increases of borderline significance	Papillary adenomas	Lynch *et al.*, 1957.
Asbestos	Rats	42–146 mg/m³	Up to 14.3 mo	Positive	Adenocarcinomas; fibrosarcomas; squamous cell carcinomas	Gross *et al.*, 1967.
Crocidolite and chrysotile asbestos	Guinea pigs, hamsters, rabbits, rats	48 mg/m³	Up to 48 mo	Negative except for 2 tumors in crocidolite exposed rats	—	Reeves *et al.*, 1971.
Amosite, crocidolite, or chrysotile asbestos	Gerbils, guinea pigs, mice, rats	48–50 mg/mm³	Up to 24 mo	Positive only in rats	Adenocarcinomas; mesotheliomas	Reeves *et al.*, 1971.
Amosite, anthophyllite, crocidolite, chrysotile asbestos	Rats, Wistar SPF	9.7–14.7 mg/m³	1 Day, 3, 6, 12 or 24 mo	Positive	Adenomas; adenocarcinomas	Wagner *et al.*, 1974.
Chrysotile asbestos, italian talc	Rats, Wistar SPF	10.8 mg/m³	6 and 12 mo	Positive in group exposed 12 mo to chrysotile	Adenomas; adenocarcinomas	Wagner *et al.*, 1977.
Chrysotile asbestos with or without cigarette smoke	Hamsters, Syrian Golden ENG:ELA	23 mg/m³	11 mo	Positive	Adenomas	Wehner *et al.*, 1977b.
Amosite, chrysotile and crocidolite asbestos	Rats, Han SPF	2–10 mg/m³	12 mo	Positive	Adenomas; adenocarcinomas	Wehner *et al.*, 1977b.
Free radicals with or without SO_2	Mice, LX	190 mg/m³ (500 ppm) SO_2	Lifetime	Some increase but significance not stated	Adenomas	Peacock and Spence, 1967.
Silica dust	Rats, Wistar, guinea pigs, rabbits	53 mg/m³	12–24 mo	Negative	—	Schepers *et al.*, 1957b.
Glass dust, quartz dust, kaolin	Rats, Carworth Farms, guinea pigs	17–27 mg/m³	12 mo	Negative	—	Gross *et al.*, 1960.
Talc	Hamsters, Syrian Golden ENG:ELA	37 mg/m³	10 mo	Negative	—	Wehner *et al.*, 1977b.
A wide variety of industrially important inorganic chemicals	Rats	Not reported	Usually 18–20 mo	Negative: only one tumor among over 1400 exposed animals	—	Schepers, 1971.

the Amosite-exposed group, 4 in the Crocidolite group, and 3 in the Chrysotile group.

The tumorigenicity of a variety of asbestos types was also investigated by Wagner *et al.* (1974). Wistar SPF rats of both sexes were exposed 7 hr/day, 5 days/week for 1 day and 3, 6, 12, or 24 months to amosite, anthophyllite, crocidolite, Canadian chrysotile, and Rhodesian chrysotile at a concentration of 9.7–14.7 mg/m^3 and then held for a lifetime. Group sizes varied from 49 to 52 for the 1-day and 3-month groups and from 19 to 28 for the three longer exposures. Averaging over asbestos types, 7/126 controls, 17/219 exposed 1 day, 67/184 exposed 3 months, 25/95 exposed 6 months, 78/129 exposed 12 months, and 63/95 exposed 24 months developed lung tumors. Differences in incidence between asbestos types were small, but of the 20 that metastasized, 16 occurred after exposure to chrysotile. The tumors present included 113 adenomas, 50 adenocarcinomas, 49 adenomatosis, 40 squamous carcinomas, and 11 mesotheliomas. Wagner *et al.* (1977) also compared the tumorigenic effects of asbestos and talc. Twenty-four Wistar SPF rats, 12 of each sex/group, were exposed to either chrysotile asbestos or Italian talc at a mean concentration of 10.8 mg/m^3, 7.5 hr/day, 5 days/week for 6 or 12 months and then held for up to a lifetime. No tumors were detected among controls and only 1 adenomatosis was found in a rat exposed 6 months to chrysotile. In the 12-month exposure groups, 3 adenomas, 2 adenomatoses and 1 adenocarcinoma were detected in the chrysotile group while 1 adenoma was detected in the talc group.

Wehner *et al.* (1975a) exposed 51 male ENG:ELA Syrian Golden hamsters/group to either chrysotile asbestos, 23 mg/m^3, 7 hr/day, 5 days/week or a combination of the same concentration of asbestos plus cigarette smoke, three times daily, 5 days/week for 11 months. The animals wre then held for a lifetime. Seven pulmonary adenomas were detected in the chrysotile exposed group, 3 in the combination exposures and none in controls. In the most recent study reported to date, Davis *et al.* (1978) exposed 48 HAN SPF rats/group 7 hr/day, 5 days/week for 1 year to chrysotile, 2 and 10 mg/m^3; crocidolite, 5 and 10 mg/m^3; or amosite, 10 mg/m^3. Forty per group were held for up to 860 days. Tumors were reported in 17 rats exposed to 10 mg/m^3 chrysotile, 9 exposed to 2 mg/m^3 chrysotile, 3 exposed to 5 mg/m^3 crocidolite, 1 exposed to 10 mg/^{3} crocidolite, and 2 exposed to 10 mg/m^3 Amosite. The tumor types included 18 pulmonary adenomas, 7 adenocarcinomas, 3 squamous cell carcinomas, 1 pleural mesothelioma, and 1 peritoneal mesothelioma.

Free radicals. Peacock and Spence (1967) exposed lung-tumor-sensitive LX mice, 60–70/group with about equal numbers of each sex, to free radicals 3 hr/day, or free radicals + SO_2 (500 ppm) 5 min/day, 5 days/week for a lifetime. Lung tumors were detected in 31, 41, and 54% of males exposed to clean air, free radicals, or free radicals + SO_2, respectively. Among females, the percentages equalled 17, 23, and 43. The statistical significance of the differences was not discussed. Most tumors were pulmonary adenomas.

Nitrogen dioxide. Richters and Kuraitis (1981) examined the influence of inhaled NO_2 upon the metastasis of blood-borne cancer cells. Following injection of melanoma cells, male C57B1 mice, 30/group, were exposed to either clean air or 0.8 ppm NO_2 8 hr/day, 5 days/week for 12 weeks. At the end of exposure the

lungs of the NO_2-exposed animals contained a significantly greater number of melanoma nodules than the lungs of control animals ($P < 0.0025$).

Silicates. Schepers *et al.* (1957a) exposed male and female Wistar rats, guinea pigs, and rabbits 8 hr/day, 5 days/week to silica dust at a concentration of 53 mg/m^3. Groups were exposed 12–24 months and held for varying periods up to 13 months in clean air. No lung tumors were detected in any of the 60 rats, 82 guinea pigs, or 10 rabbits thus exposed. Gross *et al.* (1960) exposed 40 Carworth Farms rats and 15 guinea pigs/group 6 hr/day, 5 days/week for 12 months to glass dust (17–18 mg/m^3), quartz dust (21–24 mg/m^3), or kaolin (23–27 mg/m^3). No respiratory tract tumors were detected among any of the groups.

Talc. Wehner *et al.* (1977b) exposed 50 male and 50 female ELA:ENG Syrian hamsters/group to talc at a concentration of 37 mg/m^3 with a respirable fraction equalling 8–10 mg/m^3. Individual groups were exposed 3, 30, or 150 min/day, 5 days/week for 30 days or 30 and 150 min/day for 300 days and held for a lifetime. No lung tumors were detected in any of the groups.

Miscellaneous. Schepers (1971) exposed rats to a wide variety of aerosols. These were generally airborne pollutants found primarily in industrial settings. The types of aerosols studied included quartz dust, silica, chrysotile, perlite, kaylo, fiberglass, chalcedony, chert, diatomite, fluorspars, gypsum, hematite, iron oxide, phosgene, polyester resin, etc. The strain or sex of rats, dust concentration, exposure times, etc. were usually not given. Exposure duration was generally 18–20 months. The only lung tumor detected among more than 1400 exposed rats was in an animal exposed to quartz dust in combination with dietary-induced hypovitaminasis.

VI. COMPLEX MIXTURES

Cigarette smoke. Experiments involving inhalation of cigarette smoke are summarized in Table 5.

The earliest investigation designed to evaluate the carcinogenicity of cigarette smoke was conducted by Campbell (1936). Seventy-five mice of a mixed strain/group were exposed to the smoke from 6 cigarettes twice daily, 5 days/week for a lifetime. The smoke was diluted with 50–75 parts clean air. Seventeen exposed vs. 11 controls developed tumors, a difference of borderline significance. Lorenz *et al.* (1942) reported no increase in lung tumors using strain A mice of both sexes exposed from 25 to 250 days to smoke diluted to a particulate concentration of 100 μg/m^3. Lung tumors were found in 91% of 23 surviving male and female strain A mice exposed to the smoke from 1 cigarette/hr over a 12-hr period daily for 1 year vs. 59% of 32 surviving controls ($P < 0.01$) (Essenberg, 1952). In a repeat study A/JAX mice of both sexes were exposed under similar conditions, 6 days/week, for 1 year. The only difference was the use of cigarettes with a low nicotine content (0.78%) (Essenberg *et al.*, 1955). Eighteen of 28 exposed vs. 12 of 30 controls developed lung tumors, again a significant difference. Addition of arsenic to the tobacco of a separate group did not alter the results significantly (Essenberg *et al.*, 1956).

Essenberg (1954) also investigated the potential tumor-inducing effects of cigarette paper by exposing A/JAX mice of both sexes, 36–38/group, for 1 year to

TABLE 5

INDUCTION OF RESPIRATORY TRACT TUMORS BY CIGARETTE SMOKE INHALATION

Type of exposure	Species and strain	Duration of exposure	Tumorigenic response	Primary tumor type(s)	Reference
Whole cigarette smoke	Mice, mixed strains	Lifetime	Negative	—	Campbell, 1936.
Whole cigarette smoke	Mice, A	7.5 mo	Negative	—	Lorenz *et al.*, 1942.
Whole cigarette smoke	Mice, A	≈10 mo	Positive	Pulmonary adenoma	Essenberg, 1952.
Whole cigarette smoke	Mice, A	≈10 mo	Insignificant increase	Pulmonary adenoma	Essenberg, 1955.
Whole cigarette smoke	Mice, O2O/DBA	24 mo	Positive	Pulmonary adenoma	Muhlbock, 1955.
Whole cigarette smoke	Mice, Albino	2.5–25 mo	Significant increase in 25-mo group	Pulmonary adenoma	Otto, 1963.
Whole cigarette smoke alone or plus influenza virus	Mice, C57B1	Lifetime	Small but significant increase, not potentiated by influenza virus	Alveogenic adenocarcinoma	Harris and Negroni, 1966, 1967.
Whole or filtered cigarette smoke	Mice, C57B1	Lifetime	A significant increase with whole smoke only	Pulmonary adenoma; adenocarcinoma	Harris *et al.*, 1974.
Whole cigarette smoke or vapor phase only	Mice, C57B1, Snells	Lifetime	Whole smoke and vapor phase positive in Snells	Pulmonary adenoma; adenocarcinoma	Leuchtenberger and Leuchtenberger, 1974.
Whole cigarette smoke	Rat, Wistar	Up to 24 mo	Positive	Buccal neoplasms; pulmonary adenoma	Guerin, 1959.
Whole cigarette smoke	Rat	6 mo	Some increase; significance uncertain	Pulmonary adenoma	Mori, 1964.
Whole cigarette smoke	Rat, Wistar SPF	Lifetime	Negative	—	Davis *et al.*, 1975.
Whole cigarette smoke	Rat, Fischer 344	32 mo	Positive	Pulmonary adenoma; alveogenic carcinoma	Dalbey *et al.*, 1980.
Whole cigarette smoke	Rat, Fischer 344	24 mo	Negative	—	Wehner *et al.*, 1981.
Whole cigarette smoke	Hamster, Syrian	Lifetime	Negative	—	Dontenwill, 1970.
Whole cigarette smoke alone or plus DMBA	Hamster, Syrian	Lifetime	Negative	—	Dontenwill *et al.*, 1973.
Whole cigarette smoke alone, + vit A deficiency or + DENA	Hamster, Syrian	Lifetime	Negative	—	Dontenwill *et al.*, 1977.

TABLE 5—*Continued*

Type of exposure	Species and strain	Duration of exposure	Tumorigenic response	Primary tumor type(s)	Reference
Whole cigarette smoke alone, + vit A deficiency or + DENA	Hamster, Syrian	Lifetime	Positive	Laryngeal carcinoma	Kobayashi *et al.*, 1974.
Whole cigarette smoke alone or + DMBA	Hamster, Syrian	Lifetime	Negative	—	Wehner *et al.*, 1976.
Whole cigarette smoke alone + BaP or + DMBA	Hamster, Syrian	11 mo	A small but significant increase only with smoke + DMBA	Laryngeal carcinoma	Hoffman *et al.*, 1979.
Whole cigarette smoke	Hamster, Syrian Bio 15.16	Up to 23 mo	Highly significant increase	Laryngeal carcinoma	Bernfeld *et al.*, 1974.
Whole cigarette smoke using tobacco mixed with cytrel	Hamster, Syrian Bio 15.16	Up to 23 mo	Clearcut dose-response depending on % tobacco in cigarettes	Laryngeal carcinoma	Bernfeld *et al.*, 1974.

smoke from burning 108 papers/day. Eight carcinomas and 5 adenomas were detected in exposed mice vs. 5 carcinomas and 6 adenomas in controls. Interpretation of Essenberg's data is made difficult by the high percentage of lung tumors in controls. The high incidence of tumors is undoubtedly due to their advanced age at sacrifice. In the standard strain-A protocol, the mice are normally sacrificed at 9 months of age when the control tumor incidence usually reaches ≈25% (Shimkin and Stoner, 1975).

Mühlbock (1955) exposed 020/DBA mice of both sexes to cigarette smoke 5 times/day, every 2 hours, 5.5 days/week for 2 years. Seventy-nine percent of 29 smoke-exposed survivors, compared with 31% of 321 surviving controls, developed lung tumors, a difference that was considered significant. All the tumors were carcinomas of alveolar origin. Otto (1963) exposed inbred albino mice to smoke from 12 cigarettes daily for 2.5–25 months. Twenty-one of 219 exposed mice, including 11 of 30 exposed for 24 months, developed pulmonary adenomas compared with 3 of 60 controls. Pretreatment with an 0.5-ml saturated solution of 3,4 benz(*a*)pyrene by intraperitoneal injection did not increase the incidence of lung tumors.

Harris and Negroni (1966, 1967) reported a 4% incidence of lung tumors among 100 male and 100 female C57BL mice exposed to smoke from 12 cigarettes every other day for a lifetime, compared with none in controls. No further increases were noted in groups concomitantly exposed to benz(*a*)pyrene or influenza virus aerosols. In a followup study (Harris *et al.*, 1974), equal numbers of C57BL males and females were exposed to smoke from 20 cigarettes/day. Of mice surviving more than 1 year, 10 of 326 exposed to smoke vs. 4 of 319 breathing room air developed pulmonary adenomas or carcinomas. Although differences in lung tumor incidence in these studies were small, they were highly significant ($P < 0.002$). The C57BL strain is highly resistant to the development of lung tumors and has a very low historic incidence. Thus, even small increases are often significant.

Leuchtenberger and Leuchtenberger (1970, 1974) exposed Snell's and C57BL mice, 200 or more/group equally divided by sex, daily to whole cigarette smoke or to the vapor-phase alone, for a lifetime. Among the C57BL groups, 1 control compared with 1 of the exposed mice developed a pulmonary adenoma. Among Snell's mice, 21 adenomas and 30 carcinomas were detected in animals exposed to whole smoke vs. 12 adenomas and 32 carcinomas in the vapor-phase group and 22 adenomas plus 13 carcinomas in controls. The incidence of pulmonary carcinoma was significantly increased in both the whole-smoke group ($P < 0.05$) and the vapor-phase group ($P < 0.005$).

The first tobacco-smoke-inhalation studies using hamsters were described by Dontenwill (1970). Much of this work involved testing for tolerance to smoke and the development of adequate smoking machines. No increase in cancer incidence was reported in the studies although precancerous lesions were described. A large study was conducted by Dontenwill *et al.* (1973), in which a total of 4440 hamsters were exposed to either clean air or cigarette smoke from a variety of tobaccos. Generally, 160 animals/group, divided equally by sex, were exposed to smoke from 30 cigarettes/session, twice daily, 5 days/week for a lifetime. None of the

groups exposed to tobacco smoke alone developed bronchial or tracheal tumors. Among 600 exposed to various smoking regimes, only 4 pharyngeal tumors were detected compared with 2 among controls. In a later study (Dontenwill *et al.*, 1977) using an experimental design and technique similar to those in their earlier studies, increases in lung cancer were not detected even in groups with a Vitamin A deficiency, which has been demonstrated to increase susceptibility to oral cancer in humans (Rowe and Gorlin, 1959), lung cancer in humans (Bjelke, 1975), and lung cancer in rats intratracheally instilled with 3-methylcholanthrene (Nettesheim and Williams, 1976).

The lack of clear-cut evidence for tumor induction in hamsters by inhalation of cigarette smoke resulted in attempts to demonstrate the tumor-promoting ability of cigarette smoke. This was performed by treating the animals with a known tumor initiator early in the study. One group of hamsters received an intratracheal instillation of 500 μg dimethylbenzanthracene (DMBA), while another group was injected with 10 mg/kg body wt diethylnitrosame (DENA) at the start of smoke inhalation (Dontenwill *et al.*, 1973). Tobacco-smoke inhalation failed to enhance the tumorigenic effect of either of these compounds. Kobayashi *et al.* (1974) exposed male hamsters, 25/group, to a 1:7 dilution of cigarette smoke from 6 cigarettes daily, 5 days/week for 48 weeks; to 2 mg DMBA intratracheally, divided into two equal doses; or to cigarette smoke plus DMBA. Neither DMBA nor smoking alone resulted in tumor development, but 5 laryngeal tumors were detected among 25 animals exposed to the combined treatment.

Wehner *et al.* (1976) exposed 50 male hamsters/group to cigarette smoke, 10 min/day, 3 times daily, 5 days/week, for a lifetime; to 3 mg DENA; or to cigarette smoke plus DENA. DENA induced epithelial lesions and some laryngeal papillomas, which were potentiated by cigarette smoke, but no invasive carcinomas were detected in any of the groups. Hoffman *et al.* (1979) exposed 40 hamsters/group to smoke alone, two 10-min periods/day, 5 days/week for 48 weeks; to 2 intratracheal instillations of 120 mg DMBA; to 2 instillations of 5 mg BaP on a hematite carrier; or to a combination of smoke plus initiator. Three squamous cell carcinomas of the larynx were detected among 40 animals exposed to cigarette smoke plus DMBA. None were detected in any of the other groups.

In general, lifetime exposure to cigarette smoke failed to produce increases in lung cancer in Syrian hamsters. Even the use of initiators failed to produce dramatic results. This could have been due to a lack of sensitivity or, as has been suggested by data in many of these studies, because the lifetime of the hamsters was too short for the observed lesions to progress to a cancerous state. During the past several years an attempt was made to overcome this problem by developing a strain of hamster sensitive to lung tumor induction (Homburger, 1979; Homburger *et al.*, 1979a, b). One of these strains, Bio 15.16, has shown a greatly increased susceptibility to the induction of laryngeal cancer (Bernfeld *et al.*, 1974). Among groups of ≈100 animals each, exposed to cigarette smoke twice daily, 5 days/week, for up to 100 weeks, cancer was detected in 19% of the Bio 15.16 hamsters compared with none in noninbred strains. In a more recent study using the Bio 15.16 strain, invasive laryngeal carcinomas were induced in 36.8% of smoke exposed animals (Bernfeld *et al.*, 1979). Moreover, by replacing the

cigarette tobacco with 20, 50, and 100% Cytrel, a noncarcinogenic tobacco supplement, a positive association between tobacco content and laryngeal neoplasia was observed.

Guerin (1959) reported the first apparently successful attempt to induce lung tumors in rats by cigarette smoke inhalation. Three malignant and 2 benign neoplasms of the oral cavity, plus 3 adenomas and 1 squamous carcinoma of the lung were detected among 68 rats exposed to cigarette smoke for up to 2 years, compared with 1 adenoma among controls. Two adenomas among 14 rats exposed to cigarette smoke for up to 186 days were reported by Mori (1964). These adenomas, however, were unlikely to be related to the exposure conditions because of the short length of the study. Davis *et al.* (1975) exposed Wistar SPF rats to smoke from two cigarettes/day, 5 days/week for a lifetime. Four of 406 smoke-exposed rats developed squamous cell neoplasms, 1 of which was malignant, compared with none in 197 controls or in 84 rats given a single intratracheal instillation of 2 mg 3,4-benz(*a*)pyrene. Despite the zero incidence in the controls, however, the authors did not consider the differences to be significant. Wehner *et al.* (1981) exposed 80 female Fischer 344 rats/group to the smoke from 8 cigarettes/day over a 16-hr day, 7 days/week for 24 months. Separate groups received smoke from low tar, low nicotine; low tar, medium nicotine; or high tar, high nicotine cigarettes. Although the incidence of squamous metaplasia was quite high, only one case of epidermoid carcinoma was detected in any of the exposed groups.

A serious hindrance towards exposure of rats to a great enough concentration of cigarette smoke to produce lung cancer was their susceptibility to the acute toxic effects of cigarette smoke (Dontenwill, 1970). Kendrick *et al.* (1976a) attempted to overcome this problem by gradually increasing the number of cigarettes/day at a weekly rate of 1 cigarette/day to a final level of 7–10/day. No tumors were reported in 17 female Fischer 344 rats dying after 15 months exposure or less. After 33 months of exposure, however, 5 pulmonary adenomas and 5 adenocarcinomas, alveogenic carcinomas, or squamous carcinomas were detected in 80 surviving female Fischer 344 rats vs. 1 alveogenic carcinoma among 93 controls ($P < 0.05$) (Dalbey *et al.*, 1980).

Ambient Air and Smog. Experiments involving inhalation of complex mixtures other than cigarette smoke are summarized in Table 6. The potential carcinogenic effects of ambient air particulate was first studied by McDonald and Woodhouse (1942). Particulate was collected from air-purifying screens and used for bedding. By stirring at regular intervals a dense cloud was produced. Albino mice were exposed in this manner for 47 weeks. Twenty-two percent of 57 exposed survivors vs. 15.8% of 44 surviving controls developed pulmonary adenomas, an increase of borderline significance. Gardner *et al.* (1970) exposed over 7000 mice of A, A/J, and C57BL strains to either Los Angeles air or clean, filtered air. The A and A/J mice were sacrificed after 6–18 months exposure; the C57BL mice were exposed for a lifetime. The overall incidence of lung tumors was not significantly increased in any of the three groups. In a related study, Emik *et al.* (1971) exposed C57BL mice, 150 of each sex, and A/J mice, 300 males and 280 females, to either ambient air at Riverside, California, or clean, filtered air. The C57BL mice were

TABLE 6
ONCOGENIC RESPONSE FROM INHALATION OF COMPLEX MIXTURES OTHER THAN CIGARETTE SMOKE

Pollutant	Species and strain	Exposure levels	Duration of exposure	Response	Primary tumor types	References
Ambient air particulate	Mice, Albino	Not specified	10.8 mo	Tumor increase of borderline significance	Pulmonary adenomas	McDonald and Wood-house, 1942.
Ambient air	Mice, A, A/J and C57BL	—	6–18 mo for A strains; lifetime for C57BLs	Negative	—	Gardner *et al.*, 1970.
Ambient air	Mice, A, A/J and C57BL	—	A strains sacrificed at 12–23 mo of age; lifetime for C57BLs	Negative	—	Emik *et al.*, 1971.
Ambient air	Mice, C3H	—	Lifetime	Negative	—	Peacock, 1962.
Artificial smog	Mice, A	1–3.8 ppm oxidant	12 mo	Positive	Pulmonary adenomas	Kotin and Falk, 1956.
Artificial smog	Mice, C57BL	1–3.8 ppm oxidant	Lifetime	Small but significant increase, $P < 0.05$	Pulmonary adenomas	Kotin *et al.*, 1958.
Artificial smog	Mice, C57BL	24–30 ppm gasoline + 1 ppm ozone	Lifetime	Positive	Pulmonary adenomas and adenocarcinomas	Nettesheim *et al.*, 1970.
Artificial smog	Hamsters, Syrian Golden	40–45 methane equivalents	Lifetime	Negative	—	Nettesheim *et al.*, 1975.
Gasoline engine emissions	Mice	Diluted to produce CO levels of 500 ppm	Lifetime	Negative	—	Campbell, 1936.
Diesel engine emissions	Hamsters, Syrian Golden	Diluted to produce CO levels of 50 ppm	Lifetime	Negative	—	Cross *et al.*, 1978.
Diesel engine emissions	Mice, A	1:9 or 1:18 dilutions	>7.5 mo	Negative	—	Orthoefer *et al.*, 1981; Pepelko *et al.*, 1982.
Diesel engine emissions, coal dust, or both	Rats	Diesel emissions diluted to produce 8.3 mg/m^3 particulate; coal dust, 5.8–14.9 mg/m^3	20 mo	Small increase in diesel or diesel + coal dust, significance not reported	Bronchiolar adenomas	Karagianes *et al.*, 1980.
Diesel engine emissions alone or combined with tumor promoters or initiators	Mice, Sencar	1:9 dilution	15 mo	A small but significant increase with diesel emissions alone	Pulmonary adenomas	Campbell *et al.*, 1981.

TABLE 6—*Continued*

Pollutant	Species and strain	Exposure levels	Duration of exposure	Response	Primary tumor types	References
Coal tar fumes	Rats, Bethesda black	Not reported	24 mo	Negative	—	Hueper and Payne, 1960.
Petroleum asphalt smoke	Mice, C57BL	Not reported	21 mo	Negative	—	Simmers, 1964.
Coal tar fumes	Mice, A, C3H	1.4 mg/m^3	7–12 mo	Positive, large increase in both strains	Pulmonary adenomas	Mestizova and Kossey, 1961.
Soft coal flue dust	Mice, Buffalo	Uncertain, dust was used as bedding	Lifetime	An apparent increase but significance not reported	Adenocarcinomas	Seelig and Benignus, 1936.
Lamp black	Mice, C57BL	Uncertain, dust was used as bedding	10 mo	Negative	—	Seelig and Benignus, 1938.
Carbon black	Mice, CFW, C3H	1.6 and 2.4 mg/m^3	Lifetime	Negative	—	Nau *et al.*, 1962.
Dust from tarred roads	Mice	Uncertain	11 mo	Significant increase in skin but not lung tumors	Skin tumors	Campbell, 1934.
Coal tar aerosol	Mice, C3H	300 mg/m^3	Up to 8.3 mo	An apparent increase but significance not reported	Pulmonary adenomas	Horton *et al.*, 1962.
Petroleum asphalt aerosol	Mice, C57BL	Not reported	Up to 18.5 mo	Negative	—	Simmers, 1964.
Coal tar aerosols	Mice, C3H/HeJ	120 mg/m^3	12.7 mo	Positive	Pulmonary adenomas and adenocarcinomas	Tye and Stemmer, 1967.
Diesel engine lubricating oil aerosol	Rats, Albino	132 mg/m^3	12 mo	Negative	—	Lushbaugh and Grun, 1980.
White mineral oil aerosol	Mice, CF1, CAF/JAX; hamsters, Syrian Golden; rats, Sprague–Dawley	5 and 100 mg/m^3	12–26 mo	Negative	—	Wagner *et al.*, 1964.

exposed for a lifetime; mice from the other two groups were sacrificed periodically between 12 and 23 months of age. The incidence of lung tumors was not significantly altered by exposure to ambient air in either of the A strains. Adenomas were found in 3 C57BL mice exposed to ambient air vs. 1 in filtered air, a difference that was not significant but was considered suspicious. Peacock (1962) also failed to detect an increase in lung tumor frequency among 100 male C3H mice/group exposed to either clean filtered air or unfiltered air of Central Glascow, Scotland.

The first study using an artificial smog produced by reacting ozone with a gasoline aerosol was conducted by Kotin and Falk (1956). Strain A mice of an unreported sex, 350/group, were exposed continuously to either smog or clean air for up to 52 weeks starting at 10–12 weeks of age. The smog concentration varied from 1 to 3.8 ppm of oxidant. The most clearcut difference in lung tumor incidence occurred after 40 weeks when 63% of exposed vs. 21% of controls developed pulmonary adenomas. After 52 weeks the incidence of tumor bearing mice was 80% in exposed mice with a 49% multiple tumor incidence compared with 41% in controls and a 14% incidence of multiple tumors. A similar study, using 405 C57BL mice/group, was also conducted by Kotin and Falk (1956). The design of the study differed from the previous one in that the mice were exposed for up to a lifetime. Although only 15 tumors were found in exposed mice vs. 6 in controls the difference was considered significant ($P < 0.05$) in this tumor-resistant strain. Of at least equal interest was the detection of 37 extrapulmonary tumors in control mice vs. 6 in exposed, a difference that was highly significant.

Nettesheim *et al.* (1970) exposed 545 C57BL mice/group, half of each sex, 5.5 hr/day, 5 days/week for a lifetime to either clean air or artificial smog. The smog was produced by an aerosol of 24–30 ppm gasoline and a maximum of 1 ppm ozone. One-half of the animals in each group were infected with PR-8 influenza virus 2 weeks prior to the start of inhalation exposure. In non-virus-treated mice, 5 controls vs. 14 exposed mice developed lung tumors; in the virus-treated mice, 0 controls vs. 6 exposed mice developed lung tumors. The primary tumor types were adenomas and adenocarcinomas. Nettesheim *et al.* (1975) exposed 135 male Syrian Hamsters/group 6 hr/day, 5 days/week for a lifetime to ferric oxide dust (40 mg/m^3), synthetic smog (40–45 methane equivalents), or ferric oxide and smog, either with or without prior treatment with a known carcinogen, DENA. Exposure to smog, ferric oxide, or the combination failed to induce the development of lung tumors. Neither pollutant potentiated the tumorigenic effects of DENA, and the combination of smog and ferric oxide actually inhibited the tumorigenic effect of DENA.

Engine emissions. Campbell (1936) conducted the first experiments designed to test the carcinogenic effects of inhaled engine exhaust pollutants. Groups of 75 mixed-breed mice, equally divided among sexes, were exposed 7 hr/day, 5 days/week for a lifetime to exhaust from a gasoline engine burning unleaded gasoline, diluted to produce a carbon monoxide level near 0.05%. Nine of 75 exposed to exhaust vs. 8 of 75 breathing clean air developed lung tumors. In a similar experiment using leaded gasoline 12 mice breathing exhaust vs. 6 breathing clean air developed lung tumors, an insignificant difference.

Cross *et al.* (1978) exposed male Syrian hamsters, 102 animals/group, to diesel engine emissions diluted to produce a CO level of 50 ppm, 6 hr/day, 5 days/week for a lifetime. None of the hamsters developed lung tumors. Notably, of an additional 400 animals/group exposed to radon daughters or uranium ore plus diesel engine emissions, malignant tumors were detected in only 4 hamsters. The study showed the hamster to be highly refractory to induction of pulmonary carcinomas.

A series of studies were conducted by Orthoefer *et al.* (1981) and Pepelko (1982) to evaluate the effects of inhaled diesel engine emissions upon lung tumor induction in strain A mice. A/strong or A/Jax mice were exposed 8 hr/day, 7 days/week to emissions from a Nissan 6-Cylinder diesel engine diluted with either 9 or 18 parts clean air. The mice were generally exposed from 6 weeks to 9 months of age. No differences in lung tumor incidence were noted between groups of over 400 males exposed to either a 1:18 dilution of exhaust or clean air. Among ≈68 females/group, however, 25% of exposed mice vs. 7% of controls developed pulmonary adenomas ($P < 0.05$). Among groups of half males and half females exposed to a 1:9 dilution of exhaust, only 9 of 80 exposed mice vs. 21 of 87 controls developed tumors, a difference that was significant ($P < 0.05$). Following pretreatment with 5 mg of the lung-tumor initiator urethane, 42 of 75 exposed vs. 66 of 75 clean air controls developed lung tumors ($P < 0.001$). In a final study in which half the mice of each sex were exposed to a 1:9 dilution of exhaust in the dark (to increase the likelihood they would be awake during exposure), 59 of 237 survivors in clean air vs. only 22 of 250 exposed to diesel exhaust developed lung tumors. Again the difference was highly significant ($P < 0.001$). From these studies, it appeared that inhalation of diesel engine emissions inhibited lung tumor development.

Karagianes *et al.* (1980) exposed 18 rats/group 6 hr/day, 5 days/week for 20 months to diesel engine exhaust diluted to produce 50 ppm CO, resulting in 5.3 mg/m^3 particulate concentration; coal dust (6.6 mg/m^3); coal dust (14.9 mg/m^3); or coal dust (5.8 mg/m^3) plus diesel engine emissions (8.3 mg/m^3 particulate). Four of 36 rats exposed to diesel emissions or diesel emissions plus coal dust developed lung tumors compared with none in 36 rats exposed to coal dust alone or clean air. Finally, Campbell *et al.* (1981) reported preliminary results of a study in which Sencar mice were exposed from conception to 15 months of age at a 1:9 dilution (≈12 mg/m^3 particulate) of diesel engine emissions. About 780 mice/group equally divided between sexes were exposed 8 hr/day, 7 days/week to either clean air or diesel engine emissions. One-third of each group received no further treatment, one-third received an initiating dose of urethane, and one-third received treatment throughout most of the exposure period with the lung-tumor promoter butylated hydroxytolulene (BHT). Among groups exposed to clean air or diesel exhaust alone, 16.3% of exposed females vs. 7.2% of controls ($P < 0.01$) developed lung tumors. For males and females combined, lung tumors were detected in 11.2% of exposed v. 5.6% of control mice ($P < 0.02$). Among groups treated with BHT, 18.1% of females breathing clean air vs. 6.5% exposed diesel exhaust developed lung tumors ($P < 0.03$). No other differences were significant. The majority of the tumors were pulmonary adenomas or adenocarcinomas.

Other fossil-fuel-derived smoke and fumes. Hueper and Payne (1960) were unable to detect an increase in the lung tumor incidence in 65 female Bethesda Black

rats exposed to an unspecified concentration of coal tar fumes 4 days/week for 2 years. Only one bronchial adenoma was detected among 30 C57BL mice exposed 6–7.5 hr/day, 5 days week for 21 months to smoke from petroleum asphalt produced by heating the asphalt to 121°C (250°F) (Simmers, 1964). Mestizova and Kossey (1961), however, reported increases in the lung tumor incidence in mice exposed daily for up to 1 year to coal tar fumes at a concentration of ≈1.4 mg/m^3. Among 99 Strain A mice/group an average of 9.0 tumors/mouse were reported after 7–10 months exposure compared with 0.22 in controls. Among 144 C3H mice/group, the incidence averaged 2.0 tumors/mouse after 7–10 months exposure and 5.8 tumors/mouse after 11–12 months exposure, compared with an average of 0.3 in mice held in clean air for 11–12 months.

Dusts and solid aerosols. Seelig and Benignus (1936) exposed 100 Buffalo-strain mice to flue dust from Kentucky soft coal by using the dust as bedding. Eight of 100 exposed mice vs. 1 of 50 controls exposed for a lifetime developed lung tumors. The statistical significance of this difference was not determined. In a similar study, Seelig and Benignus (1938) exposed 100 C57BL mice from 6 through 16 months of age to bedding composed of lampblack. No lung tumors were detected among the 6 mice surviving the entire exposure period. Campbell (1934) exposed mice for 332 days to dust from tarred roads. A dust cloud was generated 6 times daily, 5 days/week with foot bellows. Of 100 exposed mice, 59 developed skin tumors and 11 developed lung tumors compared with no skin tumors and 6 lung tumors among 90 controls. Although the increase in skin tumor incidence was significant in exposed mice, lung tumor rates were not detectably different from controls. Campbell (1943) summarized the results of a series of exposures similar to the one reported above. Of the dusts containing fossil fuel products, one tarred-road-dust sample produced a highly significant increase in lung tumor incidence; another one produced a definitely significant increase. Bituminous coal produced an increase of borderline significance; exhaust soot and coal soot did not produce significant enhancement of lung tumorigenesis. Actual probability values were not listed. Nau *et al.* (1962) exposed an unreported number of CFW (white) and C3H (brown) mice 7 hr/day, 5 days/week for a lifetime to either channel black (2.4 mg/m^3) or furnace black (1.6 mg/m^3). No lung tumors were detected following exposure to either substance.

Liquid aerosols. No lung tumors were detected in 10 male or 10 female C57BL mice exposed 30 min/day, 5 days/week for up to 80 weeks to an aerosol of petroleum asphalt (Simmers, 1964). Exposure of C3H mice for 1 hr/day, 3 days/week to a coal tar aerosol at a concentration of 300 mg/m^3 resulted in lung tumors in 2 of 10 mice exposed 12 to 25 weeks and in 3 of 10 exposed 34 to 36 weeks, compared with none in controls. The primary tumor types were adenomas with one malignancy detected (Horton *et al.*, 1963). Among groups of 50 male C3H/HeJ mice exposed 2 hr/day, 3 days/week for 55 weeks to aerosols of various blends of coal tars at a concentration of 120 mg/m^3, the lung tumor incidences equalled 12, 16, 18, 14, and 14 for the 5 groups compared with none in controls. Adenocarcinomas varied from 0–3/group with the remainder being pulmonary adenomas (Tye and Stemmer, 1967). No lung tumors were detected in albino rats exposed daily for 1 year to diesel engine lubricating oil at a concentration of 132 mg/m^3 (Lushbaugh *et al.*, 1950). Wagner *et al.* (1964) also reported no increase

in lung tumor incidence among male Holtzman, Sprague–Dawley rats (80/group), CF_1 mice (60/group), CAF_1/JAX mice (250/group), or Syrian Golden hamsters (106–112/group) exposed to 5 and 100 mg/m^3 white mineral oil 6 hr/day, 5 days/week for periods of 1 year to 26 months.

VII. SUMMARY AND CONCLUSIONS

It is now apparent that cancer of the respiratory tract can be induced in small laboratory animals by a wide variety of vapors, dusts, and aerosols. What is much less certain is how well the results predict carcinogenic potency of the test substances in humans. Since the majority of the experiments are concerned with testing of chemicals for human safety, the ability to extrapolate animal data to humans is of prime importance.

Comparisons of the relative carcinogenic potency of inhaled chemicals between humans and laboratory animals are usually limited by a lack of epidemiological data and/or accurate exposure assessment in humans. In most cases in which a carcinogenic effect had been detected in humans, a positive response was also found in laboratory animals. Examples include asbestos (Selikoff *et al.*, 1979) and bis-chloromethyl ether (Sakabe, 1973).

Positive responses in laboratory animals, on the other hand, are not often accompanied by similar findings in humans. One of the most likely reasons is a lack of human studies. Second, even though human studies are available, exposures may not have been at a sufficient concentration or of adequate duration to induce positive effects. Third, effects may have occurred in humans, but due to the limited size of the exposure group, deficiencies in the design or conduct of the experiment, effects were not detected. Finally, it is possible, in some instances, that humans are less sensitive than the test animals. Beryllium is an example of a potent animal carcinogen that for many years had not been shown definitively to induce lung cancer in humans (Shapely, 1977). More recent epidemiological studies by Infante *et al.* (1980) and Mancuso (1980), however, have shown that beryllium does cause lung cancer in beryllium-industry workers, pointing out that humans are not necessarily less sensitive to this chemical than animals.

In cases such as beryllium exposure where results were positive in animals but, until recently, not definitively so in humans, regulation based on animal data, if in error, will likely err on the protective side. Of greater concern are those instances where humans may be more sensitive than experimental animals. As an example, while the epidemiological evidence linking cigarette smoking in humans with lung cancer is quite strong, success in inducing lung cancer in small laboratory animals was very limited until the development of a strain of hamsters sensitive to the induction of laryngeal carcinomas (Homburger, 1979). While such instances may be few, lack of adequate human data could result in inadequate regulation.

There are several possible reasons for variations in responsiveness between laboratory animals and humans. The target organs may differ in inherent sensitivity. Such variation can even be found within a species. Strain A mice, on one hand, are highly susceptible to the induction of lung cancer, while C57BLs are

highly resistant (Shimkin and Stoner, 1975; Bickerton, 1974). While the mechanisms may not always be known for certain, they are likely to be due to the inducibility of xenobiotic-metabolizing enzyme systems, immunological factors, efficiency of DNA repair mechanisms, or other, as yet unknown factors.

Another important variable affecting responsiveness is the concentration of the test substance at the critical target organ. The anatomy of the respiratory system can have a large effect on this variable. Most laboratory species are mandatory nose breathers with a more efficient system for filtering out particulates than humans. Raabe *et al.* (1975) has shown that pulmonary bronchial deposition of particles <0.2 μm in diameter averaged 21% in hamsters and 27% in rats, while in humans the amount deposited following inhalation of similar size particles would be predicted to be near 50% (Bain and Valberg, 1976).

Concentrations at the target organ can also be influenced by exposure patterns. Humans are generally exposed at irregular intervals to varying concentrations as opposed to most animal experiments with regular exposure intervals and constant exposure levels. Humans are also quite often exposed while working or exercising with a concomitant increase in the rate and depth of respiration, resulting in increasing deposition in the deep lung. Experimental animals, on the other hand, not only are seldom forced to exercise during exposure but, being nocturnal in most cases, are usually exposed during normal sleeping hours when respiration is minimal. Finally, while humans may voluntarily inhale certain pollutants such as cigarette smoke deeply, experimental animals often respond in the opposite manner. For example, Kendrick *et al.* (1976b) has shown that hamsters greatly reduced minute volume ventilation when exposed to cigarette smoke.

Despite the limitations in the use of animal-inhalation experiments to predict the likelihood of cancer induction in humans, and despite the fact that such tests are expensive and time consuming, there are no clearcut better alternatives at present. Intratracheal instillation eliminates the need for expensive inhalation-exposure facilities. This method, however, results in intermittent exposure, often to high peak concentrations, and in less even lung distribution, sometimes inducing focal lung damage (Stenback *et al.*, 1976), and thus does not mimic inhalation exposure adequately, especially for volatile organic chemicals. Moreover, this method still requires long-term experiments. Methods such as those utilizing tracheal explants or tracheal cell cultures (Terzaghi and Nettesheim, 1979) are still in developmental stages. *In vitro* test systems, while promising and very useful as an aid in the selection of chemicals for further testing, bypass the pharmacokinetic factors involved in whole-animal testing and thus are not suitable for direct extrapolation to humans. As a result, long-term inhalation studies are likely to continue into the forseeable future, hopefully with the aid of new strains that more closely mimic humans in terms of tumor types, pharmacokinetic factors, and metabolic processes affecting susceptibility.

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